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Felts et al.

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(54) **SACCHARIDE PROTECTIVE COATING FOR PHARMACEUTICAL PACKAGE**

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(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,274,267 A 9/1966 Chow
3,297,465 A 1/1967 Connell
(Continued)

FOREIGN PATENT DOCUMENTS

AT 414209 B 10/2006
AT 504533 A1 6/2008
(Continued)

OTHER PUBLICATIONS

US 5,645,643, 07/1997, Thomas (withdrawn)
(Continued)

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(57) **ABSTRACT**

A method for providing a saccharide based lubricating or protective coating or layer on a substrate surface is provided.
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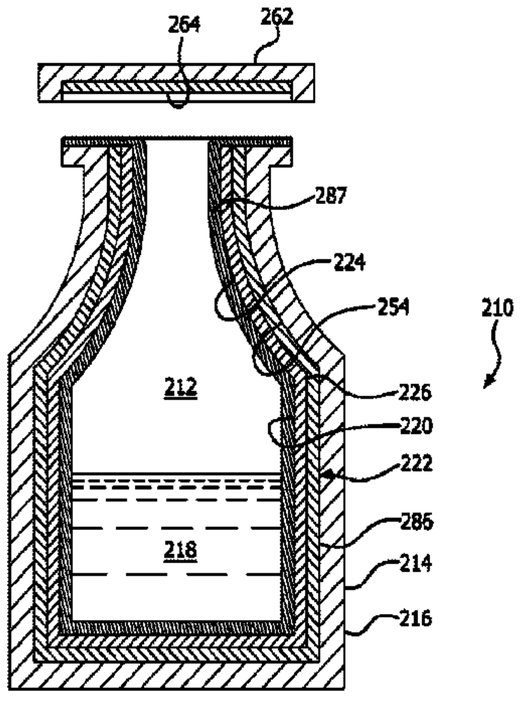

In particular, a lubricity and/or protective coating or layer made by said method is provided. Pharmaceutical packages or other vessels coated by said method and the use of such pharmaceutical packages or other vessels protecting a compound or composition contained or received in said vessel with a protective coating against mechanical and/or chemical effects of the surface of the vessel without a protective coating material are also provided.

20 Claims, 7 Drawing Sheets

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(58) **Field of Classification Search**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,355,947	A	12/1967	Karlby
3,442,686	A	5/1969	Jones
3,448,614	A	6/1969	Muger
3,590,634	A	7/1971	Pasternak
3,838,598	A	10/1974	Tomkins
3,957,653	A	5/1976	Blecher
4,111,326	A	9/1978	Percarpio
4,134,832	A	1/1979	Heimreid
4,136,794	A	1/1979	Percapio
4,162,528	A	7/1979	Maldonado et al.
4,168,330	A	9/1979	Kaganowicz
4,186,840	A	2/1980	Percarpio
4,187,952	A	2/1980	Percarpio
4,226,333	A	10/1980	Percarpio
4,289,726	A	9/1981	Potoczky
4,290,534	A	9/1981	Percarpio
4,293,078	A	10/1981	Percarpio
4,338,764	A	7/1982	Percarpio
4,391,128	A	7/1983	McWhorter
4,392,218	A	7/1983	Plunkett, Jr.
4,422,896	A	12/1983	Class
4,452,679	A	6/1984	Dunn
4,478,873	A	10/1984	Masso
4,481,229	A	11/1984	Suzuki
4,483,737	A	11/1984	Mantei
4,484,479	A	11/1984	Eckhardt
4,486,378	A	12/1984	Hirata
4,522,510	A	6/1985	Rosencwaig
4,524,616	A	6/1985	Drexel
4,552,791	A	11/1985	Hahn
4,576,204	A	3/1986	Smallborn
4,609,428	A	9/1986	Fujimura
4,610,770	A	9/1986	Saito
4,648,107	A	3/1987	Latter
4,648,281	A	3/1987	Morita
4,652,429	A	3/1987	Konrad
4,664,279	A	5/1987	Obrist
4,667,620	A	5/1987	White
4,668,365	A	5/1987	Foster
4,683,838	A	8/1987	Kimura
4,697,717	A	10/1987	Grippi
4,703,187	A	10/1987	Hofling
4,716,491	A	12/1987	Ohno
4,721,553	A	1/1988	Saito
4,725,481	A	2/1988	Ostapchenko
4,741,446	A	5/1988	Miller
4,756,964	A	7/1988	Kincaid
4,767,414	A	8/1988	Williams
4,778,721	A	10/1988	Sliemers
4,799,246	A	1/1989	Fischer
4,808,453	A	2/1989	Romberg
4,809,876	A	3/1989	Tomaswick
4,824,444	A	4/1989	Nomura
4,841,776	A	6/1989	Kawachi
4,842,704	A	6/1989	Collins
4,844,986	A	7/1989	Karakelle
4,846,101	A	7/1989	Montgomery
4,853,102	A	8/1989	Tateishi
4,869,203	A	9/1989	Pinkhasov
4,872,758	A	10/1989	Miyazaki
4,874,497	A	10/1989	Matsuoka
4,880,675	A	11/1989	Mehta
4,883,686	A	11/1989	Doehler
4,886,086	A	12/1989	Etchells
4,894,256	A	1/1990	Gartner
4,894,510	A	1/1990	Nakanishi
4,897,285	A	1/1990	Wilhelm
4,926,791	A	5/1990	Hirose
4,948,628	A	8/1990	Montgomery
4,973,504	A	11/1990	Romberg
4,991,104	A	2/1991	Miller
4,999,014	A	3/1991	Gold
5,000,994	A	3/1991	Romberg
5,016,564	A	5/1991	Nakamura
5,021,114	A	6/1991	Saito
5,028,566	A	7/1991	Lagendijk
5,030,475	A	7/1991	Ackermann
5,032,202	A	7/1991	Tsai
5,039,548	A	8/1991	Hirose
5,041,303	A	8/1991	Wertheimer
5,042,951	A	8/1991	Gold
5,044,199	A	9/1991	Drexel
5,064,083	A	11/1991	Alexander
5,067,491	A	11/1991	Taylor
5,079,481	A	1/1992	Moslehi
5,082,542	A	1/1992	Moslehi
5,084,356	A	1/1992	Deak
5,085,904	A	2/1992	Deak
5,099,881	A	3/1992	Nakajima
5,113,790	A	5/1992	Geisler
5,120,966	A	6/1992	Kondo
5,131,752	A	7/1992	Yu
5,144,196	A	9/1992	Gegenwart
5,154,943	A	10/1992	Etzkorn
5,189,446	A	2/1993	Barnes
5,192,849	A	3/1993	Moslehi
5,198,725	A	3/1993	Chen
5,203,959	A	4/1993	Hirose
5,204,141	A	4/1993	Roberts
5,209,882	A	5/1993	Hattori
5,216,329	A	6/1993	Pelleteir
5,224,441	A	7/1993	Felts
5,225,024	A	7/1993	Hanley
5,232,111	A	8/1993	Burns
5,252,178	A	10/1993	Moslehi
5,260,095	A	11/1993	Affinito
5,266,398	A	11/1993	Hioki
5,271,274	A	12/1993	Khuri-Yakub
5,272,417	A	12/1993	Ohmi
5,272,735	A	12/1993	Bryan
5,275,299	A	1/1994	Konrad
5,286,297	A	2/1994	Moslehi
5,292,370	A	3/1994	Tsai
5,294,011	A	3/1994	Konrad
5,294,464	A	3/1994	Geisler
5,298,587	A	3/1994	Hu
5,300,901	A	4/1994	Krummel
5,302,266	A	4/1994	Grabarz
5,308,649	A	5/1994	Babacz
5,314,561	A	5/1994	Komiya

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,320,875	A		6/1994	Hu
5,321,634	A		6/1994	Obata
5,330,578	A		7/1994	Sakama
5,333,049	A		7/1994	Ledger
5,338,579	A		8/1994	Ogawa et al.
5,346,579	A		9/1994	Cook
5,354,286	A		10/1994	Mesa
5,356,029	A		10/1994	Hogan
5,361,921	A		11/1994	Burns
5,364,665	A		11/1994	Felts
5,364,666	A		11/1994	Williams
5,372,851	A		12/1994	Ogawa et al.
5,374,314	A		12/1994	Babacz
5,378,510	A		1/1995	Thomas
5,395,644	A		3/1995	Affinito
5,396,080	A		3/1995	Hannotiau
5,397,956	A		3/1995	Araki
5,409,782	A		4/1995	Murayama
5,413,813	A		5/1995	Cruse
5,423,915	A		6/1995	Murata
5,429,070	A		7/1995	Campbell
5,433,786	A		7/1995	Hu
5,434,008	A		7/1995	Felts
5,439,736	A		8/1995	Nomura
5,440,446	A		8/1995	Shaw
5,443,645	A		8/1995	Otoshi
5,444,207	A		8/1995	Sekine
5,449,432	A		9/1995	Hanawa
5,452,082	A		9/1995	Sanger
5,468,520	A		11/1995	Williams
5,470,388	A		11/1995	Goedicke
5,472,660	A		12/1995	Fortin
5,485,091	A		1/1996	Verkuil
5,486,701	A		1/1996	Norton
5,494,170	A		2/1996	Burns
5,494,712	A		2/1996	Hu
5,495,958	A		3/1996	Konrad
5,508,075	A		4/1996	Roulin
5,510,155	A		4/1996	Williams
5,513,515	A		5/1996	Mayer
5,514,276	A		5/1996	Babcock
5,521,351	A		5/1996	Mahoney
5,522,518	A		6/1996	Konrad
5,531,060	A		7/1996	Fayet
5,531,683	A		7/1996	Kriesel
5,536,253	A		7/1996	Haber
5,543,919	A		8/1996	Mumola
5,545,375	A		8/1996	Tropsha
5,547,508	A		8/1996	Affinito
5,547,723	A		8/1996	Williams
5,554,223	A		9/1996	Imahashi
5,555,471	A		9/1996	Xu
5,565,248	A		10/1996	Plester
5,569,810	A		10/1996	Tsuji
5,571,366	A		11/1996	Ishii
5,578,103	A		11/1996	Araujo
5,591,898	A		1/1997	Mayer
5,593,550	A		1/1997	Stewart
5,597,456	A		1/1997	Maruyama
5,616,369	A		4/1997	Williams
5,620,523	A		4/1997	Maeda
5,632,396	A		5/1997	Burns
5,633,711	A		5/1997	Nelson
5,643,638	A		7/1997	Otto
5,652,030	A		7/1997	Delperier
5,654,054	A		8/1997	Tropsha
5,656,141	A		8/1997	Betz
5,658,438	A		8/1997	Givens
5,665,280	A		9/1997	Tropsha
5,667,840	A		9/1997	Tingey
5,674,321	A		10/1997	Pu
5,677,010	A		10/1997	Esser
5,679,412	A		10/1997	Kuehnle
5,679,413	A		10/1997	Petrmichl
5,683,771	A		11/1997	Tropsha
5,686,157	A		11/1997	Harvey
5,690,745	A		11/1997	Grunwald
5,691,007	A		11/1997	Montgomery
5,693,196	A		12/1997	Stewart
5,699,923	A		12/1997	Burns
5,702,770	A		12/1997	Martin
5,704,983	A		1/1998	Thomas
5,716,683	A		2/1998	Harvey
5,718,967	A		2/1998	Hu
5,725,909	A		3/1998	Shaw
5,733,405	A		3/1998	Taki
5,736,207	A		4/1998	Walther
5,737,179	A		4/1998	Shaw
5,738,233	A		4/1998	Burns
5,738,920	A		4/1998	Knors
5,744,360	A		4/1998	Hu
5,750,892	A		5/1998	Huang
5,763,033	A		6/1998	Tropsha
5,766,362	A		6/1998	Montgomery
5,769,273	A		6/1998	Sasaki
5,779,074	A		7/1998	Burns
5,779,716	A		7/1998	Cano
5,779,802	A		7/1998	Borghs
5,779,849	A		7/1998	Blalock
5,788,670	A		8/1998	Reinhard
5,792,940	A		8/1998	Ghandhi
5,798,027	A		8/1998	Lefebvre
5,800,880	A		9/1998	Laurent
5,807,343	A		9/1998	Tucker
5,807,605	A		9/1998	Tingey
5,812,261	A		9/1998	Nelson
5,814,257	A		9/1998	Kawata
5,814,738	A		9/1998	Pinkerton
5,820,603	A		10/1998	Tucker
5,823,373	A		10/1998	Sudo
5,824,198	A		10/1998	Williams
5,824,607	A		10/1998	Trow
5,833,752	A		11/1998	Martin
5,837,888	A		11/1998	Mayer
5,837,903	A		11/1998	Weigand
5,840,167	A		11/1998	Kim
5,853,833	A	*	12/1998	Sudo B32B 1/02 220/62.22
5,855,686	A		1/1999	Rust
5,861,546	A		1/1999	Sagi
5,871,700	A		2/1999	Konrad
5,877,895	A		3/1999	Shaw
5,880,034	A		3/1999	Keller
5,888,414	A		3/1999	Collins
5,888,591	A		3/1999	Gleason
5,897,508	A		4/1999	Konrad
5,900,284	A		5/1999	Hu
5,900,285	A		5/1999	Walther
5,902,461	A		5/1999	Xu
5,904,952	A		5/1999	Lopata
5,913,140	A		6/1999	Roche
5,914,189	A		6/1999	Hasz
5,919,328	A		7/1999	Tropsha
5,919,420	A		7/1999	Niermann
5,935,391	A		8/1999	Nakahigashi
5,945,187	A		8/1999	Buch-Rasmussen
5,951,527	A		9/1999	Sudo
5,952,069	A		9/1999	Tropsha
5,955,161	A		9/1999	Tropsha
5,961,911	A		10/1999	Hwang
5,968,620	A		10/1999	Harvey
5,972,297	A		10/1999	Niermann
5,972,436	A		10/1999	Walther
5,985,103	A		11/1999	Givens
6,001,429	A		12/1999	Martin
6,009,743	A		1/2000	Mayer
6,013,337	A		1/2000	Knors
6,017,317	A		1/2000	Newby
6,018,987	A		2/2000	Mayer
6,020,196	A		2/2000	Hu
6,027,619	A		2/2000	Cathey
6,032,813	A		3/2000	Niermann
6,035,717	A		3/2000	Carodiskey
6,050,400	A		4/2000	Taskis

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,051,151	A	4/2000	Keller
6,054,016	A	4/2000	Tuda
6,054,188	A	4/2000	Tropsha
6,068,884	A	5/2000	Rose
6,077,403	A	6/2000	Kobayashi
6,081,330	A	6/2000	Nelson
6,082,295	A	7/2000	Lee
6,083,313	A	7/2000	Venkatraman et al.
6,085,927	A	7/2000	Kusz
6,090,081	A	7/2000	Sudo
6,106,678	A	8/2000	Shufflebotham
6,110,395	A	8/2000	Gibson, Jr.
6,110,544	A	8/2000	Yang
6,112,695	A	9/2000	Felts
6,116,081	A	9/2000	Ghandhi
6,117,243	A	9/2000	Walther
6,118,844	A	9/2000	Fischer
6,125,687	A	10/2000	McClelland
6,126,640	A	10/2000	Tucker
6,136,275	A	10/2000	Niermann
6,139,802	A	10/2000	Niermann
6,143,140	A	11/2000	Wang
6,149,982	A	11/2000	Plester
6,153,269	A	11/2000	Gleason
6,156,152	A	12/2000	Ogino
6,156,399	A	12/2000	Spallek
6,156,435	A	12/2000	Gleason
6,160,350	A	12/2000	Sakemi
6,161,712	A	12/2000	Savitz
6,163,006	A	12/2000	Doughty
6,165,138	A	12/2000	Miller
6,165,542	A	12/2000	Jaworowski
6,165,566	A	12/2000	Tropsha
6,171,670	B1	1/2001	Sudo
6,175,612	B1	1/2001	Sato
6,177,142	B1	1/2001	Felts
6,180,185	B1	1/2001	Felts
6,180,191	B1	1/2001	Felts
6,188,079	B1	2/2001	Juvinall
6,189,484	B1	2/2001	Yin
6,190,992	B1	2/2001	Sandhu
6,193,853	B1	2/2001	Yumshtyk
6,196,155	B1	3/2001	Setoyama
6,197,166	B1	3/2001	Moslehi
6,200,658	B1	3/2001	Walther
6,200,675	B1	3/2001	Neerinck
6,204,922	B1	3/2001	Chalmers
6,210,791	B1	4/2001	Skoog
6,214,422	B1	4/2001	Yializis
6,217,716	B1	4/2001	Fai Lai
6,223,683	B1	5/2001	Plester
6,236,459	B1	5/2001	Negahdaripour
6,245,190	B1	6/2001	Masuda
6,248,219	B1	6/2001	Wellerdieck
6,248,397	B1	6/2001	Ye
6,251,792	B1	6/2001	Collins
6,254,983	B1	7/2001	Namiki
6,261,643	B1	7/2001	Hasz
6,263,249	B1	7/2001	Stewart
6,271,047	B1	8/2001	Ushio
6,276,296	B1	8/2001	Plester
6,277,331	B1	8/2001	Konrad
6,279,505	B1	8/2001	Plester
6,284,986	B1	9/2001	Dietze
6,306,132	B1	10/2001	Moorman
6,308,556	B1	10/2001	Sagi
6,322,661	B1	11/2001	Bailey, III
6,331,174	B1	12/2001	Reinhard et al.
6,346,596	B1	2/2002	Mallen
6,348,967	B1	2/2002	Nelson
6,350,415	B1	2/2002	Niermann
6,351,075	B1	2/2002	Barankova
6,352,629	B1	3/2002	Wang
6,354,452	B1	3/2002	DeSalvo
6,355,033	B1	3/2002	Moorman
6,365,013	B1	4/2002	Beele
6,375,022	B1	4/2002	Zurcher
6,376,028	B1	4/2002	Laurent
6,379,757	B1	4/2002	Iacovangelo
6,382,441	B1	5/2002	Carano
6,394,979	B1	5/2002	Sharp
6,396,024	B1	5/2002	Doughty
6,399,944	B1	6/2002	Vasilyev
6,402,885	B2	6/2002	Loewenhardt
6,410,926	B1	6/2002	Munro
6,413,645	B1	7/2002	Graff
6,432,494	B1	8/2002	Yang
6,432,510	B1	8/2002	Kim
6,470,650	B1	10/2002	Lohwasser
6,471,822	B1	10/2002	Yin
6,475,622	B2	11/2002	Namiki
6,482,509	B2	11/2002	Buch-Rasmussen et al.
6,486,081	B1	11/2002	Ishikawa
6,500,500	B1	12/2002	Okamura
6,503,579	B1	1/2003	Murakami
6,518,195	B1	2/2003	Collins
6,524,448	B2	2/2003	Brinkmann
6,539,890	B1	4/2003	Felts
6,544,610	B1	4/2003	Minami
6,551,267	B1	4/2003	Cohen
6,558,679	B2	5/2003	Flament-Garcia et al.
6,562,189	B1	5/2003	Quiles
6,565,791	B1	5/2003	Laurent
6,582,426	B2	6/2003	Moorman
6,582,823	B1	6/2003	Sakhrani et al.
6,584,828	B2	7/2003	Sagi
6,595,961	B2	7/2003	Hetzler
6,597,193	B2	7/2003	Lagowski
6,599,569	B1	7/2003	Humele
6,599,594	B1	7/2003	Walther
6,602,206	B1	8/2003	Niermann
6,616,632	B2	9/2003	Sharp
6,620,139	B1	9/2003	Plicchi
6,620,334	B2	9/2003	Kanno
6,623,861	B2	9/2003	Martin
6,638,403	B1	10/2003	Inaba
6,638,876	B2	10/2003	Levy
6,645,354	B1	11/2003	Gorokhovsky
6,651,835	B2	11/2003	Iskra
6,652,520	B2	11/2003	Moorman
6,656,540	B2	12/2003	Sakamoto
6,658,919	B2	12/2003	Chatard
6,662,957	B2	12/2003	Zurcher
6,663,601	B2	12/2003	Hetzler
6,670,200	B2	12/2003	Ushio
6,673,199	B1	1/2004	Yamartino
6,680,091	B2	1/2004	Buch-Rasmussen et al.
6,680,621	B2	1/2004	Savtchouk
6,683,308	B2	1/2004	Itagaki
6,684,683	B2	2/2004	Potyrailo
6,702,898	B2	3/2004	Hosoi
6,706,412	B2	3/2004	Yializis
6,746,430	B2	6/2004	Lubrecht
6,749,078	B2	6/2004	Iskra
6,752,899	B1	6/2004	Singh
6,753,972	B1	6/2004	Hirose
6,757,056	B1	6/2004	Kudinar
6,764,714	B2	7/2004	Wei
6,765,466	B2	7/2004	Miyata
6,766,682	B2	7/2004	Engle
6,774,018	B2	8/2004	Mikhael
6,796,780	B1	9/2004	Chatard
6,800,852	B2	10/2004	Larson
6,808,753	B2	10/2004	Rule
6,810,106	B2	10/2004	Sato
6,815,014	B2	11/2004	Gabelnick
6,818,310	B2	11/2004	Namiki
6,827,972	B2	12/2004	Darras
6,837,954	B2	1/2005	Carano
6,844,075	B1	1/2005	Saak
6,853,141	B2	2/2005	Hoffman
6,858,259	B2	2/2005	Affinito
6,863,731	B2	3/2005	Elsayed-Ali
6,864,773	B2	3/2005	Perrin

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,866,656	B2	3/2005	Tingey
6,872,428	B2	3/2005	Yang
6,876,154	B2	4/2005	Appleyard
6,885,727	B2	4/2005	Tamura
6,887,578	B2	5/2005	Gleason
6,891,158	B2	5/2005	Larson
6,892,567	B1	5/2005	Morrow
6,899,054	B1	5/2005	Bardos
6,905,769	B2	6/2005	Komada
6,910,597	B2	6/2005	Iskra
6,911,779	B2	6/2005	Madocks
6,919,107	B2	7/2005	Schwarzenbach
6,919,114	B1	7/2005	Darras
6,933,460	B2	8/2005	Vanden Brande
6,946,164	B2	9/2005	Huang
6,952,949	B2	10/2005	Moore
6,960,393	B2	11/2005	Yializis
6,962,671	B2	11/2005	Martin
6,965,221	B2	11/2005	Lipcsei
6,981,403	B2	1/2006	Ascheman
6,989,675	B2	1/2006	Kesil
6,995,377	B2	2/2006	Darr
7,029,755	B2	4/2006	Terry
7,029,803	B2	4/2006	Becker
7,039,158	B1	5/2006	Janik
7,052,736	B2	5/2006	Wei
7,052,920	B2	5/2006	Ushio
7,059,268	B2	6/2006	Russell
7,067,034	B2	6/2006	Bailey, III
7,074,501	B2	7/2006	Czeremuszkin
7,098,453	B2	8/2006	Ando
7,109,070	B2	9/2006	Behle
7,112,352	B2	9/2006	Schaepkens
7,112,541	B2	9/2006	Xia
7,115,310	B2	10/2006	Jacoud
7,118,538	B2	10/2006	Konrad
7,119,908	B2	10/2006	Nomoto
7,121,135	B2	10/2006	Moore
7,130,373	B2	10/2006	Omote
7,150,299	B2	12/2006	Hertzler
7,160,292	B2	1/2007	Moorman
7,180,849	B2	2/2007	Hirokane
7,183,197	B2	2/2007	Won
7,188,734	B2	3/2007	Konrad
7,189,290	B2	3/2007	Hama
7,193,724	B2	3/2007	Isei
7,198,685	B2	4/2007	Hetzler
7,206,074	B2	4/2007	Fujimoto
7,244,381	B2	7/2007	Chatard
7,253,892	B2	8/2007	Semersky
7,286,242	B2	10/2007	Kim
7,288,293	B2	10/2007	Koulik
7,297,216	B2	11/2007	Hetzler
7,300,684	B2	11/2007	Boardman
7,303,789	B2	12/2007	Saito
7,303,790	B2	12/2007	Delaunay
7,306,852	B2	12/2007	Komada
7,332,227	B2	2/2008	Hardman
7,338,576	B2	3/2008	Ono
7,339,682	B2	3/2008	Aiyer
7,344,766	B1	3/2008	Sorensen
7,348,055	B2	3/2008	Chappa
7,348,192	B2	3/2008	Mikami
7,362,425	B2	4/2008	Meeks
7,381,469	B2	6/2008	Moelle
7,390,573	B2	6/2008	Korevaar
7,399,500	B2	7/2008	Bicker
7,405,008	B2	7/2008	Domine
7,409,313	B2	8/2008	Ringermacher
7,411,685	B2	8/2008	Takashima
RE40,531	E	10/2008	Graff
7,431,989	B2	10/2008	Sakhrani
7,438,783	B2	10/2008	Miyata
7,444,955	B2	11/2008	Boardman
7,455,892	B2	11/2008	Goodwin
7,480,363	B2	1/2009	Lasiuk
7,488,683	B2	2/2009	Kobayashi
7,494,941	B2	2/2009	Kasahara
7,507,378	B2	3/2009	Reichenbach
7,513,953	B1	4/2009	Felts
7,520,965	B2	4/2009	Wei
7,521,022	B2	4/2009	Konrad
7,534,615	B2	5/2009	Havens
7,534,733	B2	5/2009	Bookbinder
RE40,787	E	6/2009	Martin
7,541,069	B2	6/2009	Tudhope
7,552,620	B2	6/2009	DeRoos
7,553,529	B2	6/2009	Sakhrani
7,555,934	B2	7/2009	DeRoos
7,569,035	B1	8/2009	Wilmot
7,579,056	B2	8/2009	Brown
7,582,868	B2	9/2009	Jiang
7,586,824	B2	9/2009	Hirokane
7,595,097	B2	9/2009	Iacovangelo
7,608,151	B2	10/2009	Tudhope
7,609,605	B2	10/2009	Hirokane
7,618,686	B2	11/2009	Colpo
7,624,622	B1	12/2009	Mayer
7,625,494	B2	12/2009	Honda
7,641,636	B2	1/2010	Moesli
7,645,696	B1	1/2010	Dulkin
7,648,481	B2	1/2010	Geiger
7,682,816	B2	3/2010	Kim
7,694,403	B2	4/2010	Moulton
7,699,933	B2	4/2010	Lizenberg
7,704,683	B2	4/2010	Wittenberg
7,713,638	B2	5/2010	Moelle
7,736,689	B2	6/2010	Chappa
7,740,610	B2	6/2010	Moh
7,744,567	B2	6/2010	Glowacki
7,744,790	B2	6/2010	Behle
7,745,228	B2	6/2010	Schwind
7,745,547	B1	6/2010	Auerbach
7,749,914	B2	7/2010	Honda
7,754,302	B2	7/2010	Yamasaki
7,766,882	B2	8/2010	Sudo
7,780,866	B2	8/2010	Miller
7,785,862	B2	8/2010	Kim
7,790,475	B2	9/2010	Galbraith
7,798,993	B2	9/2010	Lim
7,803,305	B2	9/2010	Ahern
7,807,242	B2	10/2010	Soerensen
7,815,922	B2	10/2010	Chaney
7,846,293	B2	12/2010	Iwasaki
7,854,889	B2	12/2010	Perot
7,867,366	B1	1/2011	McFarland
7,901,783	B2	3/2011	Rose
7,905,866	B2	3/2011	Haider
7,922,880	B1	4/2011	Pradhan
7,922,958	B2	4/2011	D'Arrigo
7,931,955	B2	4/2011	Behle
7,932,678	B2	4/2011	Madocks
7,934,613	B2	5/2011	Sudo
7,943,205	B2	5/2011	Schaepkens
7,947,337	B2	5/2011	Kuepper
7,955,986	B2	6/2011	Hoffman
7,960,043	B2	6/2011	Harris
7,964,438	B2	6/2011	Roca I Cabarrocas
7,967,945	B2	6/2011	Glukhoy
7,975,646	B2	7/2011	Rius
7,985,188	B2	7/2011	Felts
8,025,915	B2	9/2011	Haines
8,038,858	B1	10/2011	Bures
8,039,524	B2	10/2011	Chappa
8,056,719	B2	11/2011	Porret
8,062,266	B2	11/2011	McKinnon
8,066,854	B2	11/2011	Storey
8,070,917	B2	12/2011	Tsukamoto
8,075,995	B2	12/2011	Zhao
8,092,605	B2	1/2012	Shannon
8,101,246	B2	1/2012	Fayet
8,197,452	B2	6/2012	Harding
8,227,025	B2	7/2012	Pryce Lewis et al.
8,258,486	B2	9/2012	Avnery

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,268,410	B2	9/2012	Moelle
8,273,222	B2	9/2012	Wei
8,313,455	B2	11/2012	DiGregorio
8,323,166	B2	12/2012	Haines
8,389,958	B2	3/2013	Vo-Dinh
8,397,667	B2	3/2013	Behle
8,409,441	B2	4/2013	Wilt
8,418,650	B2	4/2013	Goto
8,435,605	B2	5/2013	Aitken et al.
8,475,886	B2	7/2013	Chen et al.
8,512,796	B2	8/2013	Felts
8,524,331	B2	9/2013	Honda
8,592,015	B2	11/2013	Bicker
8,603,638	B2	12/2013	Liu
8,618,509	B2	12/2013	Vo-Dinh
8,623,324	B2	1/2014	Diwu
8,633,034	B2	1/2014	Trotter
8,747,962	B2	6/2014	Bicker
8,802,603	B2	8/2014	D'Souza
8,816,022	B2	8/2014	Zhao
9,068,565	B2	6/2015	Alarcon
2001/0000279	A1	4/2001	Daniels
2001/0021356	A1	9/2001	Konrad
2001/0038894	A1	11/2001	Komada
2001/0042510	A1	11/2001	Plester
2001/0043997	A1	11/2001	Uddin
2002/0006487	A1	1/2002	O'Connor
2002/0007796	A1	1/2002	Gorokhovsky
2002/0070647	A1	6/2002	Ginovker
2002/0117114	A1	8/2002	Ikenaga
2002/0125900	A1	9/2002	Savtchouk
2002/0130674	A1	9/2002	Lagowski
2002/0141477	A1	10/2002	Akahori
2002/0153103	A1	10/2002	Madocks
2002/0155218	A1	10/2002	Meyer
2002/0170495	A1	11/2002	Nakamura
2002/0176947	A1	11/2002	Darras
2002/0182101	A1	12/2002	Koulik
2002/0185226	A1	12/2002	Lea
2002/0190207	A1	12/2002	Levy
2003/0010454	A1	1/2003	Bailey, III
2003/0013818	A1	1/2003	Hakuta
2003/0029837	A1	2/2003	Trow
2003/0031806	A1	2/2003	Jinks
2003/0046982	A1	3/2003	Chartard
2000/3119193		6/2003	Hess
2003/0102087	A1	6/2003	Ito
2003/0159654	A1	8/2003	Arnold
2003/0215652	A1	11/2003	O'Connor
2003/0219547	A1	11/2003	Arnold
2003/0232150	A1	12/2003	Arnold
2004/0024371	A1	2/2004	Plicchi
2004/0039401	A1	2/2004	Chow
2004/0040372	A1	3/2004	Plester
2004/0045811	A1	3/2004	Wang
2004/0050744	A1	3/2004	Hama
2004/0055538	A1	3/2004	Gorokhovsky
2004/0071960	A1	4/2004	Weber
2004/0082917	A1	4/2004	Hetzler
2004/0084151	A1	5/2004	Kim
2004/0125913	A1	7/2004	Larson
2004/0135081	A1	7/2004	Larson
2004/0149225	A1	8/2004	Weikart
2004/0177676	A1	9/2004	Moore
2004/0195960	A1	10/2004	Czeremuszkin
2004/0206309	A1	10/2004	Bera
2004/0217081	A1	11/2004	Konrad
2004/0247948	A1	12/2004	Behle
2004/0267194	A1	12/2004	Sano
2005/0000962	A1	1/2005	Crawford
2005/0010175	A1	1/2005	Beedon
2005/0019503	A1	1/2005	Komada
2005/0037165	A1	2/2005	Ahern
2005/0039854	A1	2/2005	Matsuyama
2005/0045472	A1	3/2005	Nagata
2005/0057754	A1	3/2005	Smith
2005/0073323	A1	4/2005	Kohno
2005/0075611	A1	4/2005	Hetzler
2005/0075612	A1	4/2005	Lee
2005/0161149	A1	7/2005	Yokota
2005/0169803	A1	8/2005	Betz
2005/0190450	A1	9/2005	Becker
2005/0196629	A1	9/2005	Bariatinsky
2005/0199571	A1	9/2005	Geisler
2005/0206907	A1	9/2005	Fujimoto
2005/0211383	A1	9/2005	Miyata
2005/0223988	A1	10/2005	Behle
2005/0227002	A1	10/2005	Lizenberg
2005/0227022	A1	10/2005	Domine
2005/0229850	A1	10/2005	Behle
2005/0233077	A1	10/2005	Lizenberg
2005/0233091	A1	10/2005	Kumar
2005/0236346	A1	10/2005	Whitney
2005/0260504	A1	11/2005	Becker
2005/0284550	A1	12/2005	Bicker
2006/0005608	A1	1/2006	Kutzhoffer
2006/0013997	A1	1/2006	Kuepper
2006/0014309	A1	1/2006	Sachdev
2006/0024849	A1	2/2006	Zhu
2006/0042755	A1	3/2006	Holmberg
2006/0046006	A1	3/2006	Bastion
2006/0051252	A1	3/2006	Yuan
2006/0051520	A1	3/2006	Behle
2006/0076231	A1	4/2006	Wei
2006/0086320	A1	4/2006	Lizenberg
2006/0099340	A1	5/2006	Behle
2006/0121222	A1	6/2006	Andrich
2006/0121613	A1	6/2006	Havens
2006/0121623	A1	6/2006	He
2006/0127699	A1	6/2006	Moelle
2006/0135945	A1	6/2006	Bankiewicz
2006/0138326	A1	6/2006	Jiang
2006/0150909	A1	7/2006	Behle
2006/0169026	A1	8/2006	Kage
2006/0178627	A1	8/2006	Geiger
2006/0183345	A1	8/2006	Nguyen
2006/0192973	A1	8/2006	Aiyer
2006/0196419	A1	9/2006	Tudhope
2006/0198903	A1	9/2006	Storey
2006/0198965	A1	9/2006	Tudhope
2006/0200078	A1	9/2006	Konrad
2006/0200084	A1	9/2006	Ito
2006/0210425	A1	9/2006	Mirkarimi
2006/0228497	A1	10/2006	Kumar
2006/0260360	A1	11/2006	Dick
2007/0003441	A1	1/2007	Wohleb
2007/0009673	A1	1/2007	Fukazawa et al.
2007/0017870	A1	1/2007	Belov
2007/0048456	A1	3/2007	Keshner
2007/0049048	A1	3/2007	Rauf
2007/0051629	A1	3/2007	Dolnik
2007/0065680	A1	3/2007	Schultheis
2007/0076833	A1	4/2007	Becker
2007/0102344	A1	5/2007	Konrad
2007/0123920	A1	5/2007	Inokuti
2007/0148326	A1	6/2007	Hastings
2007/0166187	A1	7/2007	Song
2007/0184657	A1	8/2007	Iijima
2007/0187229	A1	8/2007	Aksenov
2007/0187280	A1	8/2007	Haines
2007/0205096	A1	9/2007	Nagashima
2007/0215009	A1	9/2007	Shimazu
2007/0215046	A1	9/2007	Lupke
2007/0218265	A1	9/2007	Harris
2007/0224236	A1	9/2007	Boden
2007/0229844	A1	10/2007	Holz
2007/0231655	A1	10/2007	Ha
2007/0232066	A1	10/2007	Bicker
2007/0235890	A1	10/2007	Lewis
2007/0243618	A1	10/2007	Hatchett
2007/0251458	A1	11/2007	Mund
2007/0258894	A1	11/2007	Melker et al.
2007/0259184	A1	11/2007	Martin
2007/0281108	A1	12/2007	Weikart

(56) **References Cited**

U.S. PATENT DOCUMENTS

2007/0281117	A1	12/2007	Kaplan
2007/0287950	A1	12/2007	Kjeken
2007/0287954	A1	12/2007	Zhao
2007/0298189	A1	12/2007	Straemke
2008/0011232	A1	1/2008	Ruis
2008/0017113	A1	1/2008	Goto
2008/0023414	A1	1/2008	Konrad
2008/0027400	A1	1/2008	Harding
2008/0045880	A1	2/2008	Kjeken
2008/0050567	A1	2/2008	Kawashima
2008/0050932	A1	2/2008	Lakshmanan
2008/0053373	A1	3/2008	Mund
2008/0069970	A1	3/2008	Wu
2008/0071228	A1	3/2008	Wu
2008/0081184	A1	4/2008	Kubo
2008/0090039	A1	4/2008	Klein
2008/0093245	A1	4/2008	Periasamy
2008/0102206	A1	5/2008	Wagner
2008/0109017	A1	5/2008	Herweck
2008/0110852	A1	5/2008	Kuroda
2008/0113109	A1	5/2008	Moelle
2008/0118734	A1	5/2008	Goodwin
2008/0131628	A1	6/2008	Abensour
2008/0131638	A1	6/2008	Hutton
2008/0139003	A1	6/2008	Pirzada
2008/0145271	A1	6/2008	Kidambi
2008/0187681	A1	8/2008	Hofrichter
2008/0202414	A1	8/2008	Yan
2008/0206477	A1	8/2008	Rius
2008/0210550	A1	9/2008	Walther
2008/0220164	A1	9/2008	Bauch
2008/0223815	A1	9/2008	Konrad
2008/0233355	A1	9/2008	Henze
2008/0260966	A1	10/2008	Hanawa
2008/0277332	A1	11/2008	Liu
2008/0289957	A1	11/2008	Takigawa
2008/0292806	A1	11/2008	Wei
2008/0295772	A1	12/2008	Park
2008/0303131	A1	12/2008	McElrea et al.
2008/0312607	A1	12/2008	Delmotte
2008/0314318	A1	12/2008	Han
2009/0004363	A1	1/2009	Keshner
2009/0017217	A1	1/2009	Hass
2009/0022981	A1	1/2009	Yoshida
2009/0029402	A1	1/2009	Papkovsky
2009/0031953	A1	2/2009	Ingle
2009/0032393	A1	2/2009	Madocks
2009/0039240	A1	2/2009	Van Nijnatten
2009/0053491	A1	2/2009	Loboda
2009/0061237	A1	3/2009	Gates
2009/0065485	A1	3/2009	O'Neill
2009/0081797	A1	3/2009	Fadeev
2009/0099512	A1	4/2009	Digregorio
2009/0104392	A1	4/2009	Takada
2009/0117268	A1	5/2009	Lewis
2009/0117389	A1	5/2009	Amberg-Schwab
2009/0122832	A1	5/2009	Feist
2009/0134884	A1	5/2009	Bosselmann
2009/0137966	A1	5/2009	Rueckert
2009/0142227	A1	6/2009	Fuchs
2009/0142514	A1	6/2009	O'Neill
2009/0147719	A1	6/2009	Kang
2009/0149816	A1	6/2009	Hetzler
2009/0155490	A1	6/2009	Bicker
2009/0162571	A1	6/2009	Haines
2009/0166312	A1	7/2009	Giraud
2009/0176031	A1	7/2009	Armellin
2009/0220948	A1	9/2009	Oviso et al.
2009/0263668	A1	10/2009	David
2009/0280268	A1	11/2009	Glukhoy
2009/0297730	A1	12/2009	Glukhoy
2009/0306595	A1	12/2009	Shih
2009/0326517	A1	12/2009	Bork
2010/0021998	A1	1/2010	Sanyal
2010/0028238	A1	2/2010	Maschwitz
2010/0034985	A1	2/2010	Krueger
2010/0075077	A1	3/2010	Bicker
2010/0089097	A1	4/2010	Brack
2010/0105208	A1	4/2010	Winniczek
2010/0132762	A1	6/2010	Graham, Jr.
2010/0145284	A1	6/2010	Togashi
2010/0149540	A1	6/2010	Boukherroub
2010/0174239	A1	7/2010	Yodfat
2010/0174245	A1	7/2010	Halverson
2010/0178490	A1	7/2010	Cerny
2010/0186740	A1	7/2010	Lewis
2010/0190036	A1	7/2010	Komvopoulos
2010/0193461	A1	8/2010	Boutroy
2010/0195471	A1	8/2010	Hirokane
2010/0204648	A1	8/2010	Stout
2010/0230281	A1	9/2010	Park
2010/0231194	A1	9/2010	Bauch
2010/0237545	A1	9/2010	Haury
2010/0273261	A1	10/2010	Chen
2010/0275847	A1	11/2010	Yamasaki
2010/0279397	A1	11/2010	Crawford
2010/0298738	A1	11/2010	Felts
2010/0298779	A1	11/2010	Hetzler
2011/0037159	A1	2/2011	Mcelrea et al.
2011/0046570	A1	2/2011	Stout
2011/0056912	A1	3/2011	Matsuyama
2011/0065798	A1	3/2011	Hoang
2011/0079582	A1	4/2011	Yonesu
2011/0093056	A1	4/2011	Kaplan
2011/0111132	A1	5/2011	Wei
2011/0117202	A1	5/2011	Bourke, Jr.
2011/0117288	A1	5/2011	Honda
2011/0137263	A1	6/2011	Ashmead
2011/0152820	A1	6/2011	Chattaraj
2011/0159101	A1	6/2011	Kurdyumov et al.
2011/0160662	A1	6/2011	Stout
2011/0160663	A1	6/2011	Stout
2011/0174220	A1	7/2011	Laure
2011/0186537	A1	8/2011	Rodriguez San Juan
2011/0220490	A1	9/2011	Wei
2011/0253674	A1	10/2011	Chung
2011/0313363	A1	12/2011	D'Souza
2011/0319758	A1	12/2011	Wang
2011/0319813	A1	12/2011	Kamen
2012/0003497	A1	1/2012	Handy
2012/0004339	A1	1/2012	Chappa
2012/0021136	A1	1/2012	Dzengeleski
2012/0031070	A1	2/2012	Slough
2012/0035543	A1	2/2012	Kamen
2012/0052123	A9	3/2012	Kurdyumov et al.
2012/0053530	A1	3/2012	Zhao
2012/0058351	A1	3/2012	Zhao
2012/0065612	A1	3/2012	Stout
2012/0097527	A1	4/2012	Kodaira
2012/0097870	A1	4/2012	Leray
2012/0108058	A1	5/2012	Ha
2012/0123345	A1	5/2012	Felts
2012/0143148	A1	6/2012	Zhao
2012/0149871	A1	6/2012	Saxena
2012/0171386	A1	7/2012	Bicker
2012/0175384	A1	7/2012	Greter
2012/0183954	A1	7/2012	Diwu
2012/0205374	A1	8/2012	Klumpen
2012/0231182	A1	9/2012	Stevens
2012/0234720	A1	9/2012	Digregorio
2012/0252709	A1	10/2012	Felts
2013/0041241	A1	2/2013	Felts
2013/0057677	A1	3/2013	Weil
2013/0072025	A1	3/2013	Singh
2013/0081953	A1	4/2013	Bruna et al.
2013/0190695	A1	7/2013	Wu
2013/0209704	A1	8/2013	Krueger
2013/0296235	A1	11/2013	Alarcon
2014/0010969	A1	1/2014	Bicker
2014/0052076	A1	2/2014	Zhao
2014/0054803	A1	2/2014	Chen
2014/0099455	A1	4/2014	Stanley
2014/0110297	A1	4/2014	Trotter
2014/0147654	A1	5/2014	Walthe

(56) **References Cited**

U.S. PATENT DOCUMENTS

2014/0151320	A1	6/2014	Chang
2014/0151370	A1	6/2014	Chang
2014/0187666	A1	7/2014	Aizenberg
2014/0190846	A1	7/2014	Belt
2014/0221934	A1	8/2014	Janvier
2014/0251856	A1	9/2014	Larsson
2014/0305830	A1	10/2014	Bicker
2015/0165125	A1	6/2015	Foucher
2015/0224263	A1	8/2015	Dugand

FOREIGN PATENT DOCUMENTS

AU	2002354470	B2	5/2007
CA	2085805		12/1992
CA	2277679	A1	7/1997
CA	2355681		7/2000
CA	2571380	A1	7/2006
CA	27118253		9/2009
CA	2268719	C	8/2010
CN	2546041	Y	4/2003
CN	1711310	A	12/2005
CN	2766863	Y	3/2006
CN	1898172	A	1/2007
CN	201002786	Y	1/2008
CN	101147813	A	3/2008
CN	201056331	Y	5/2008
CN	102581274	A	7/2012
DE	1147836		4/1969
DE	1147838		4/1969
DE	3632748	A1	4/1988
DE	3908418	A1	9/1990
DE	4214401	C1	3/1993
DE	4204082	A1	8/1993
DE	4316349	A1	11/1994
DE	4438359		5/1996
DE	19707645	A1	8/1998
DE	19830794	A1	1/2000
DE	19912737	A1	6/2000
DE	10010831	A1	9/2001
DE	10154404	C1	6/2003
DE	10201110	A1	10/2003
DE	10242698		3/2004
DE	10246181	A1	4/2004
DE	10353540	A1	5/2004
DE	102004017236	A1	10/2005
DE	102006061585	A1	2/2008
DE	102008023027	A1	11/2009
EP	0121340	A2	10/1984
EP	0275965	A2	7/1988
EP	0284867	A2	10/1988
EP	0306307		3/1989
EP	0329041	A2	8/1989
EP	0343017	A2	11/1989
EP	0396919	A2	11/1990
EP	0482613	A1	10/1991
EP	0484746	A2	10/1991
EP	0495447	A1	7/1992
EP	0520519	A1	12/1992
EP	0535810	A1	4/1993
EP	0375778	B1	9/1993
EP	0571116	A1	11/1993
EP	0580094	A1	1/1994
EP	0603717	A2	6/1994
EP	0619178		10/1994
EP	0645470	A1	3/1995
EP	0697378	A2	2/1996
EP	0709485	B1	5/1996
EP	0719877	A1	7/1996
EP	0728676	A1	8/1996
EP	0787824	A2	8/1997
EP	0787828	A2	8/1997
EP	0814114	A1	12/1997
EP	0251812	A2	1/1998
EP	0833366	A2	4/1998
EP	0879611	A2	11/1998
EP	0940183	A2	9/1999
EP	0962229	A2	12/1999
EP	0992610	A2	4/2000
EP	1119034	A1	7/2001
EP	0954272	B1	3/2002
EP	1245694	A1	10/2002
EP	1388594	B1	1/2003
EP	1317937	A1	6/2003
EP	1365043	A1	11/2003
EP	1367145		12/2003
EP	1388593	A1	2/2004
EP	1439241	A2	7/2004
EP	1447459	A2	8/2004
EP	1990639	A1	2/2005
EP	1510595	A1	3/2005
EP	1522403	A2	4/2005
EP	1901067	A2	8/2005
EP	1507894		12/2005
EP	1507723		3/2006
EP	1653192	A1	5/2006
EP	1810758	A1	7/2007
EP	1356260	B1	12/2007
EP	1870117	A2	12/2007
EP	1881088	A1	1/2008
EP	1507887		7/2008
EP	1415018		10/2008
EP	2199264	A1	11/2009
EP	1388594	B1	1/2010
EP	2178109	A1	4/2010
EP	1507895		7/2010
EP	2218465	A1	8/2010
EP	2243751	A1	10/2010
EP	2251671		11/2010
EP	2261185		12/2010
EP	2369038	A2	9/2011
EP	1960279	B1	10/2011
EP	2602354	A1	6/2013
EP	2639330	A1	9/2013
FR	891892	A	11/1942
GB	752822		7/1956
GB	1363762		8/1974
GB	1513426	A	6/1978
GB	1566251		4/1980
GB	2210826	A	6/1989
GB	2231197	A	11/1990
GB	2246794	A	2/1992
GB	2246795	A	2/1992
GB	2387964	A	10/2003
JP	56027330	A	3/1981
JP	58154602	A	9/1983
JP	59087307	A	5/1984
JP	59154029		9/1984
JP	S61183462	A	8/1986
JP	S62180069	A	8/1987
JP	S62290866	A	12/1987
JP	63124521	A2	5/1988
JP	1023105	A	1/1989
JP	H01225775	A	9/1989
JP	1279745		11/1989
JP	2501490		5/1990
JP	3183759	A2	8/1991
JP	H03260065	A	11/1991
JP	H03271374	A	12/1991
JP	4000373	A	1/1992
JP	4000374	A	1/1992
JP	4000375	A	1/1992
JP	4014440	A	1/1992
JP	H04124273	A	4/1992
JP	H0578844	A	3/1993
JP	05-006688	A	4/1993
JP	H05263223	A	10/1993
JP	6010132	A	1/1994
JP	6289401		10/1994
JP	7041579	A	2/1995
JP	7068614	A	3/1995
JP	7126419	A	5/1995
JP	7-304127		11/1995
JP	8025244	A	1/1996
JP	8084773	A	4/1996

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

JP	H08296038	A	11/1996
JP	9005038	A	1/1997
JP	10008254	A	1/1998
JP	10-130844		5/1998
JP	11-108833	A	4/1999
JP	11106920		4/1999
JP	H11256331	A	9/1999
JP	11344316	A	12/1999
JP	2000064040	A	2/2000
JP	2000109076	A	4/2000
JP	2001033398	A	2/2001
JP	2001231841	A	8/2001
JP	2002177364	A	6/2002
JP	2002206167	A	7/2002
JP	2002371364	A	12/2002
JP	2003171771	A	6/2003
JP	2003-268550	A	9/2003
JP	2003294431	A	10/2003
JP	2003305121	A	10/2003
JP	2004002928	A	1/2004
JP	2004008509	A	1/2004
JP	2004043789	A	2/2004
JP	2004100036	A	4/2004
JP	2004156444	A	6/2004
JP	2004168359	A	6/2004
JP	2004169087	A	6/2004
JP	2004203682	A	7/2004
JP	2004-253683	A	9/2004
JP	2004307935	A	11/2004
JP	2005035597	A	2/2005
JP	2005043285	A	2/2005
JP	2005132416	A	5/2005
JP	2005160888	A	6/2005
JP	2005-200044		7/2005
JP	2005200044	A	7/2005
JP	2005-241524	A	9/2005
JP	2005271997	A	10/2005
JP	2005290561	A	10/2005
JP	2006-064416	A	3/2006
JP	2006111967	A	4/2006
JP	2006160268	A	6/2006
JP	2006-224992	A	8/2006
JP	2006249577	A	9/2006
JP	2007050898	A	3/2007
JP	2007231386	A	9/2007
JP	2007246974	A	9/2007
JP	2008174793	A	7/2008
JP	2009-062620	A	3/2009
JP	2009079298	A	4/2009
JP	2009084203	A	4/2009
JP	2009185330	A	8/2009
JP	2010155134	A	7/2010
JP	2012210315	A	11/2012
KR	10-2005-0100367	A	10/2005
KR	10-2006-0029694		4/2006
KR	10-0685594	B1	2/2007
SU	1530913		12/1989
TW	200703536	A	1/2007
WO	WO9324243	A1	12/1993
WO	WO9400247	A1	1/1994
WO	WO9426497	A1	11/1994
WO	WO95/24275		9/1995
WO	WO97/11482		3/1997
WO	WO97/13802		4/1997
WO	WO98-27926		7/1998
WO	WO98/45871		10/1998
WO	WO9917334	A1	4/1999
WO	WO99/41425		8/1999
WO	WO99/50471		10/1999
WO	WO0038566	A2	7/2000
WO	WO0104668	A1	1/2001
WO	WO0125788		4/2001
WO	WO0154816	A1	8/2001
WO	WO0156706	A1	8/2001
WO	WO0170403	A1	9/2001
WO	WO02/43116	A2	5/2002
WO	WO0249925	A1	6/2002
WO	WO02/056333	A1	7/2002
WO	WO02072914		9/2002
WO	WO02076709	A1	10/2002
WO	WO03014415	A1	2/2003
WO	WO03033426		4/2003
WO	WO03038143		5/2003
WO	WO03040649	A1	5/2003
WO	WO03044240	A1	5/2003
WO	WO2005035147	A1	4/2005
WO	WO2005/052555	A1	6/2005
WO	WO2005051525	A1	6/2005
WO	WO2005103605	A1	11/2005
WO	WO2006012281	A1	2/2006
WO	WO2006027568	A1	3/2006
WO	WO2006029743	A1	3/2006
WO	WO2006044254	A1	4/2006
WO	WO2006048276		5/2006
WO	WO2006048277	A1	5/2006
WO	WO2006069774	A1	7/2006
WO	WO2006135755	A2	12/2006
WO	WO2007028061	A2	3/2007
WO	WO2007035741	A2	3/2007
WO	WO2007036544	A1	4/2007
WO	WO2007/081814		7/2007
WO	WO2007/089216	A1	8/2007
WO	WO2007112328	A2	10/2007
WO	WO2007120507	A2	10/2007
WO	WO2007133378	A1	11/2007
WO	WO2007134347	A2	11/2007
WO	WO2008014438	A2	1/2008
WO	WO2008024566	A2	2/2008
WO	WO2008040531	A1	4/2008
WO	WO2008047541	A1	4/2008
WO	WO2008067574	A1	6/2008
WO	WO2008071458	A1	6/2008
WO	WO2008093335	A2	8/2008
WO	2008/121478	A2	10/2008
WO	WO2009/015862	A1	2/2009
WO	WO2009020550	A2	2/2009
WO	WO2009021257	A1	2/2009
WO	WO2009030974		3/2009
WO	WO2009030975	A1	3/2009
WO	WO2009030976	A1	3/2009
WO	WO2009031838	A1	3/2009
WO	WO2009040109		4/2009
WO	WO2009053947	A2	4/2009
WO	WO2009112053	A1	9/2009
WO	WO2009117032		9/2009
WO	WO2009118361	A1	10/2009
WO	WO2009158613		12/2009
WO	WO2010047825	A1	4/2010
WO	WO2010095011	A1	8/2010
WO	WO2010/132579		11/2010
WO	WO2010/132581		11/2010
WO	WO2010/132584		11/2010
WO	WO2010/132585		11/2010
WO	WO2010/132589		11/2010
WO	WO2010/132591		11/2010
WO	WO2010034004	A1	11/2010
WO	WO2010132579		11/2010
WO	WO2010132579	A2	11/2010
WO	WO2010132589		11/2010
WO	WO2010132591		11/2010
WO	WO2011029628		3/2011
WO	WO2011007055	A1	6/2011
WO	WO2011080543	A1	7/2011
WO	WO2011082296	A1	7/2011
WO	WO2011090717	A1	7/2011
WO	WO2011/143329		11/2011
WO	WO2011/143509		11/2011
WO	WO2011/143509	A1	11/2011
WO	WO2011137437		11/2011
WO	WO2011143329		11/2011
WO	WO2011159975	A1	12/2011
WO	WO2012003221		1/2012
WO	WO2012009653		1/2012

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO2013045671	A1	4/2013
WO	WO2013/071138		5/2013
WO	WO2013/071138	A1	5/2013
WO	WO2013/170044		11/2013
WO	WO2013/170052		11/2013
WO	WO2014/008138		1/2014
WO	WO2014/059012		4/2014
WO	WO2014/071061		5/2014
WO	WO2014/078666		5/2014
WO	WO2014/085346		6/2014
WO	WO2014/085348		6/2014
WO	WO2014/134577		9/2014
WO	WO2014/144926		9/2014
WO	WO2014/164928		10/2014

OTHER PUBLICATIONS

Allison, H.L., The Real Markets for Transparent Barrier Films, 37th Annual Technical Conference Proceedings, 1994, ISBN 1-878068-13-X, pp. 458.

Bailey, R. et al., Thin-Film Multilayer Capacitors Using Pyrolytically Deposited Silicon Dioxide, IEEE Transactions on Parts, Hybrids, and Packaging, vol. PHP-12, No. 4, Dec. 1976, pp. 361-364.

Banks, B.A., et al., Fluoropolymer Filled SiO2 Coatings; Properties and Potential Applications, Society of Vacuum Coaters, 35th Annual Technical Conference Proceedings, 1992, ISBN 1-878068-11-3, pp. 89-93.

Baouchi, W., X-Ray Photoelectron Spectroscopy Study of Sodium Ion Migration through Thin Films of SiO2 Deposited on Sodalime Glass, 37th Annual Technical Conference Proceedings, 1994, ISBN 1-878068-13-X, pp. 119-422.

Boebel, F. et al., Simultaneous In Situ Measurement of Film Thickness and Temperature by Using Multiple Navelengths Pyrometric Interferometry (MWPI), IEEE Transaction on Semiconductor Manufacturing, vol. 6, No. 2, May 1993, , pp. 112-118.

Bush, V. et al., The Evolution of Evacuated Blood Collection Tubes, BD Diagnostics—Preanalytical Systems Newsletter, vol. 19, No. 1, 2009.

Chahroudi, D., Deposition Technology for Glass Barriers, 33rd Annual Technical Conference Proceedings, 1990, ISBN 1-878068-09-1, pp. 212-220.

Chahroudi, D., et al., Transparent Glass Barrier Coatings for Flexible Film Packaging, Society of Vacuum Coaters, 34th Annual Technical Conference Proceedings, 1991, ISBN 1-878068-10-5, pp. 130-133.

Chahroudi, D., Glassy Barriers from Electron Beam Web Coaters, 32nd Annual Technical Conference Proceedings, 1989, pp. 29-39.

Czeremuszkin, G. et al., Ultrathin Silicon-Compound Barrier Coatings for Polymeric Packaging Materials: An Industrial Perspective, Plasmas and Polymers, vol. 6, Nos. 1/2, Jun. 2001, pp. 107-120.

Ebihara, K. et al., Application of the Dielectric Barrier Discharge to Detect Defects in a Teflon Coated Metal Surface, 2003 J. Phys. D: Appl. Phys. 36 2883-2886, doi: 10.1088/0022-3727/36/23/003, IOP Electronic Journals, http://www.iop.org/EJ/abstract/0022-3727/36/23/003, printed Jul. 14, 2009.

Egitto, F.D., et al., Plasma Modification of Polymer Surfaces, Society of Vacuum Coaters, 36th Annual Technical Conference Proceedings, 1993, ISBN 1-878068-12-1, pp. 10-21.

Erlat, A.G. et al., SIOx Gas Barrier Coatings on Polymer Substrates: Morphology and Gas Transport Considerations, ACS Publications, Journal of Physical Chemistry, published Jul. 2, 1999, http://pubs.acs.org/doi/abs/10.1021/jp990737e, printed Jul. 14, 2009.

Fayet, P., et al., Commercialism of Plasma Deposited Barrier Coatings for Liquid Food Packaging, 37th Annual Technical Conference Proceedings, 1995, ISBN 1-878068-13-X, pp. 15-16.

Felts, J., Hollow Cathode Based Multi-Component Depositions, Vacuum Technology & Coating, Mar. 2004, pp. 48-55.

Felts, J.T., Thickness Effects on Thin Film Gas Barriers: Silicon-Based Coatings, Society of Vacuum Coaters, 34th Annual Technical Conference Proceedings, 1991, ISBN 1-878068-10-5, pp. 99-104.

Felts, J.T., Transparent Barrier Coatings Update: Flexible Substrates, Society of Vacuum Coaters, 36th Annual Technical Conference Proceedings, 1993, ISBN 1-878068-12-1, pp. 324-331.

Felts, J.T., Transparent Gas Barrier Technologies, 33rd Annual Technical Conference Proceedings, 1990, ISBN 1-878068-09-1, pp. 184-193.

Finson, E, et al., Transparent SiO2 Barrier Coatings: Conversion and Production Status, 37th Annual Technical Conference Proceedings, 1994, ISBN 1-878068-13-X, pp. 139-143.

Flaherty, T. et al., Application of Spectral Reflectivity to the Measurement of Thin-Film Thickness, Opto-Ireland 2002: Optics and Photonics Technologies and Applications, Proceedings of SPIE vol. 4876, 2003, pp. 976-983.

Hora, R., et al., Plasma Polymerization: A New Technology for Functional Coatings on Plastics, 36th Annual Technical Conference Proceedings, 1993, ISBN 1-878068-12-1, pp. 51-55.

Zu, M., et al., High Performance Clear CoatTM Barrier Film, 36th Annual Technical Conference Proceedings, 1993, ISBN 1-878068-12-1, pp. 333-340.

Jost, S., Plasma Polymerized Organosilicon Thin Films on Reflective Coatings, 33rd Annual Technical Conference Proceedings, 1990, ISBN 1-878068-09-1, pp. 344-346.

Kaganowicz, G., et al., Plasma-Deposited Coatings—Properties and Applications, 23rd Annual Technical Conference Proceedings, 1980, pp. 24-30.

Kamineni, V. et al., Thickness Measurement of Thin Metal Films by Optical Metrology, College of Nanoscale Science and Engineering, University of Albany, Albany, NY.

Klemberg-Sapieha, J.E., et al., Transparent Gas Barrier Coatings Produced by Dual Frequency PECVD, 36th Annual Technical Conference Proceedings, 1993, ISBN 1-878068-12-1, pp. 445-449.

Krug, T., et al., New Developments in Transparent Barrier Coatings, 36th Annual Technical Conference Proceedings, 1993, ISBN 1-878068-12-1, pp. 302-305.

Kuhr, M. et al., Multifunktionsbeschichtungen für innovative Applikationen von Kunststoff-Substraten, HiCotec Smart Coating Solutions.

Kulshreshtha, D.S., Specifications of a Spectroscopic Ellipsometer, Department of Physics & Astrophysics, University of Delhi, Delhi-110007, Jan. 16, 2009.

Krug, T.G., Transparent Barriers for Food Packaging, 33rd Annual Technical Conference Proceedings, 1990, ISBN 1-878068-09-1, pp. 163-169.

Lee, K. et al., The Ellipsometric Measurements of a Curved Surface, Japanese Journal of Applied Physics, vol. 44, No. 32, 2005, pp. L1015-L1018.

Lelait, L. et al., Microstructural Investigations of EBPVD Thermal Barrier Coatings, Journal De Physique IV, Colloque C9, supplément au Journal de Physique III, vol. 3, Dec. 1993, pp. 645-654.

Masso, J.D., Evaluation of Scratch Resistant and Antireflective Coatings for Plastic Lenses, 32nd Annual Technical Conference Proceedings, 1989, p. 237-240.

Misiano, C., et al., New Colourless Barrier Coatings (Oxygen & Water Vapor Transmission Rate) on Plastic Substrates, 35th Annual Technical Conference Proceedings, 1992, ISBN 1-878068-11-3, pp. 28-40.

Misiano, C., et al., Silicon Oxide Barrier Improvements on Plastic Substrate, Society of Vacuum Coaters, 34th Annual Technical Conference Proceedings, 1991, ISBN 1-878068-10-5, pp. 105-112.

Mount, E., Measuring Pinhole Resistance of Packaging, Corotec Corporation website, http://www.convertingmagazine.com, printed Jul. 13, 2009.

Murray, L. et al., The Impact of Foil Pinholes and Flex Cracks on the Moisture and Oxygen Barrier of Flexible Packaging.

Nelson, R.J., et al., Double-Sided QLF® Coatings for Gas Barriers, Society of Vacuum Coaters, 34th Annual Technical Conference Proceedings, 1991, ISBN 1-878068-10-5, pp. 113-117.

Nelson, R.J., Scale-Up of Plasma Deposited SiOx Gas Diffusion Barrier Coatings, 35th Annual Technical Conference Proceedings, 1992, ISBN 1-878068-11-3, pp. 75-78.

(56) **References Cited**

OTHER PUBLICATIONS

Novotny, V. J., Ultrafast Ellipsometric Mapping of Thin Films, IBM Technical Disclosure Bulletin, vol. 37, No. 02A, Feb. 1994, pp. 187-188.
Rüger, M., Die Pulse Sind das Plus, PICVD-Beschichtungsverfahren.
Schultz, A. et al., Detection and Identification of Pinholes in Plasma-Polymerised Thin Film Barrier Coatings on Metal Foils, Surface & Coatings Technology 200, 2005, pp. 213-217.
Stchakovsky, M. et al., Characterization of Barrier Layers by Spectroscopic Ellipsometry for Packaging Applications, Horiba Jobin Yvon, Application Note, Spectroscopic Ellipsometry, SE 14, Nov. 2005.
Teboul, E., Thi-Film Metrology: Spectroscopic Ellipsometer Becomes Industrial Thin-Film Tool, LaserFocusWorld, http://www.laserfocusworld.com/display_article, printed Jul. 14, 2009.
Teyssedre, G. et al., Temperature Dependence of the Photoluminescence in Poly(Ethylene Terephthalate) Films, Polymer 42, 2001, pp. 8207-8216.
Tsung, L. et al., Development of Fast CCD Cameras for In-Situ Electron Microscopy, Microsc Microanal 14(Supp 2), 2008.
Wood, L et al., A Comparison of SiO2 Barrier Coated Polypropylene to Other Coated Flexible Substrates, 35th Annual Technical Conference Proceedings, 1992, ISBN 1-878068-11-3, pp. 59-62.
Yang, et al., Microstructure and tribological properties of SiOx/DLC films grown by PECVD, Surface and Coatings Technology, vol. 194, Issue 1, Apr. 20, 2005, pp. 128-135.
AN 451, Accurate Thin Film Measurements by High-Resoluiton Transmission Electron Microscopy (HRTEM), Evans Alalytical Group, Version 1.0, Jun. 12, 2008, pp. 1-2.
Benefits of TriboGlide, TriboGlide Silicone-Free Lubrication Systems, http://www.triboglide.com/benfits.htm, printed Aug. 31, 2009.
Coating Syringes, http://www.triboglide.com/syringes.htm, printed Aug. 31, 2009.
Coating/Production Process, http://www.triboglide.com/process.htm, printed Aug. 31, 2009.
Munich Exp, Materialica 2005: Fundierte Einblicke in den Werkstofsektor, Seite 1, von 4, ME095-6.
Schott Developing Syringe Production in United States, Apr. 14, 2009, http://www.schott.com/pharmaceutical_packaging, printed Aug. 31, 2009.
Sterile Prefillable Glass and Polymer Syringes, Schott forma vitrum, http://www.schott.com/pharmaceutical_packaging.
Transparent und recyclingfähig, neue verpackung, Dec. 2002, pp. 54-57.
European Patent Office, Communication with European Search Report, in Application No. 10162758.6, dated Aug. 19, 2010.
Griesser, Hans J., et al., Elimination of Stick-Slip of Elastomeric Sutures by Radiofrequency Glow Discharge Deposited Coatings, Biomed Mater. Res. Appl Biomater, 2000, vol. 53, 235-243, John Wiley & Sons, Inc.
European Patent Office, Communication with extended Search Report, in Application No. EP 10162761.0, dated Feb. 10, 2011.
European Patent Office, Communication with partial Search Report, in Application No. EP 10162758.6, dated Aug. 19, 2010.
European Patent Office, Communication with extended Search Report, in Application No. EP 10162758.6, dated Dec. 21, 2010.
Yang, et al., Microstructure and tribological properties of SiOx/DLC films grown by PECVD, Surface and Coatings Technology, vol. 194 (2005), Apr. 20, 2005, pp. 128-135.
European Patent Office, Communication with extended European search report, in Application No. EP10162756.0, dated Nov. 17, 2010.
Prasad, G.R. et al., "Biocompatible Coatings with Silicon and Titanium Oxides Deposited by PECVD", 3rd Mikkeli International Industrial Coating Seminar, Mikkeli, Finland, Mar. 16-18, 2006.
European Patent Office, Communication with extended European search report, in Application No. EP10162757.8, dated Nov. 10, 2010.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2010/034568, dated Jan. 21, 2011.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2010/034571, dated Jan. 26, 2011.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2010/034576, dated Jan. 25, 2011.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2010/034577, dated Jan. 21, 2011.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2010/034582, dated Jan. 24, 2011.
European Patent Office, Communication with Extended Search Report, in Application No. EP 101627552, dated Nov. 9, 2010.
European Patent Office, Communication with Extended Search Report, in Application No. EP 10162760.2, dated Nov. 12, 2010.
PCT, Written Opinion of the International Searching Authority with International Search Report in Application No. PCT/US2010/034586, dated Mar. 15, 2011.
Shimojima, Atsushi et al., Structure and Properties of Multilayered Siloxane-Organic Hybrid Films Prepared Using Long-Chain Organotrialkoxysilanes Containing C=C Double Bonds, Journal of Materials Chemistry, 2007, vol. 17, pp. 558-663, ©The Royal Society of Chemistry, 2007.
Sone, Hayato et al., Picogram Mass Sensor Using Resonance Frequency Shift of Cantilever, Japanese Journal of Applied Physics, vol. 43, No. 6A, 2004, pp. 3648-3651, © The Japan Society of Applied Physics.
Sone, Hayato et al., Femtogram Mass Sensor Using Self-Sensing Cantilever for Allergy Check, Japanese Journal of Applied Physics, vol. 45, No. 3B, 2006, pp. 2301-2304, © The Japan Society of Applied Physics.
Mallikarjunan, Anupama et al, The Effect of Interfacial Chemistry on Metal Ion Penetration into Polymeric Films, Mat. Res. Soc. Symp. Proc. vol. 734, 2003, © Materials Research Society.
Schonher, H., et al., Friction and Surface Dynamics of Polymers on the Nanoscale by AFM, STM and AFM Studies on (Bio)molecular Systems: Unravelling the Nanoworld. Topics in Current Chemistry, 2008, vol. 285, pp. 103-156, ® Springer-Verlag Berlin Heidelberg.
Lang, H.P., Gerber, C., Microcantilever Sensors, STM and AFM Studies on (Bio)molecular Systems: Unravelling the Nanoworld. Topics in Current Chemistry, 2008, vol. 285, pp. 1-28, ® Springer-Verlag Berlin Heidelberg.
Patent Cooperation Treaty, Notification of Transmittal of International Preliminary Report on Patentability, in Application No. PCT/US2010/034576, dated Sep. 14, 2011.
Patent Cooperation Treaty, Notification of Transmittal of International Preliminary Report on Patentability, in Application No. PCT/US2010/034568, dated Sep. 14, 2011.
Patent Cooperation Treaty, International Search Report and Written Opinion, in Application No. PCT/US2011/036358, dated Sep. 9, 2011.
Patent Cooperation Treaty, International Search Report and Written Opinion, in Application No. PCT/US2011/036340, dated Aug. 1, 2011.
MacDonald, Gareth, "West and Daikyo Seiko Launch Ready Pack", http://www.in-pharmatechnologist.com/Packaging/West-and-Daikyo-Seiko-launch-Ready-Pack, 2 pages, retrieved from the Internet Sep. 22, 2011.
Kumer, Vijai, "Development of Terminal Sterilization Cycle for Pre-Filled Cyclic Olefin Polymer (COP) Syringes", http://abstracts.aapspharmaceutica.com/ExpoAAPS09/CC/forms/attendee/index.aspx? content=sessionInfo&sessionId=401, 1 page, retrieved from the internet Sep. 22, 2011.
Quinn, F.J., "Biotech Lights Up the Glass Packaging Picture", http://www.pharmaceuticalcommerce.com/frontEnd/main.php?idSeccion=840, 4 pages, retrieved from the Internet Sep. 21, 2011.

(56) **References Cited**

OTHER PUBLICATIONS

Wen, Zai-Qing et al., Distribution of Silicone Oil in Prefilled Glass Syringes Probed with Optical and Spectroscopic Methods, PDA Journal of Pharmaceutical Science and Technology 2009, 63, pp. 149-158.
ZebraSci—Intelligent Inspection Products, webpage, http://zebrasci.com/index.html, retrieved from the internet Sep. 30, 2011.
Google search re "cyclic olefin polymer resin" syringe OR vial, http://www.google.com/search?sclient=psy-ab&hl=en&lr=&source=hp&q=%22cyclic+olefin+polymer+resin%22+syringe+OR+vial&btnG=Search&pbx=1&oq=%22cyclic+olefin+polymer+resin%22+syringe+OR+vial&aq, 1 page, retrieved from the internet Sep. 22, 2011.
Taylor, Nick, "West to Add CZ Vials as Glass QC Issues Drive Interest", ttp://twitter.com/WestPharma/status/98804071674281986, 2 pages, retrieved from the Internet Sep. 22, 2011.
Patent Cooperation Treaty, International Preliminary Examining Authority, Notification of Transmittal of International Preliminary Report on Patentability, in international application No. PCT/US2010/034571, dated Jun. 13, 2011.
Patent Cooperation Treaty, International Preliminary Examining Authority, Written Opinion of the International Preliminary Examining Authority, in international application No. PCT/US2010/034586, dated Aug. 23, 2011.
Patent Cooperation Treaty, International Preliminary Examining Authority, Written Opinion of the International Preliminary Examining Authority, in international application No. PCT/US2010/034568, dated May 30, 2011.
Silicone Oil Layer, Contract Testing, webpage, http://www.siliconization.com/downloads/siliconeoillayercontracttesting.pdf, retrieved from the Internet Oct. 28, 2011.
Patent Cooperation Treaty, Notification of Transmittal of International Preliminary Report on Patentability, in PCT/US2010/034577, dated Nov. 24, 2011.
Patent Cooperation Treaty, Notification of Transmittal of International Preliminary Report on Patentability, in PCT/US2010/034582, dated Nov. 24, 2011.
Patent Cooperation Treaty, Notification of Transmittal of International Preliminary Report on Patentability, in PCT/US2010/034586, dated Dec. 20, 2011.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2011/036097, dated Dec. 29, 2011.
"Oxford instruments plasmalab 80plus", XP55015205, retrieved from the Internet on Dec. 20, 2011, URL:http://www.oxfordplasma.de/pdf_inst/plas_80.pdf.
Patent Cooperation Treaty, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, in PCT/US2011/044215, dated Dec. 29, 2011.
European Patent Office, Communication pursuant to Article 94(3) EPC, in Application No. 10 162 758.6-1234, dated May 8, 2012 (6 pages).
Hanlon, Adriene Lepiane, Pak, Chung K., Pawlikowski, Beverly A., Decision on Appeal, Appeal No. 2005-1693, U.S. Appl. No. 10/192,333, dated Sep. 30, 2005.
Arganguren, Mirta I., Macosko, Christopher W., Thakkar, Bimal, and Tirrel, Matthew, "Interfacial Interactions in Silica Reinforced Silicones," Materials Research Society Symposium Proceedings, vol. 170, 1990, pp. 303-308.
Patent Cooperation Treaty, International Preliminary Examining Authority, Notification of Transmittal of International Preliminary Report on Patentability, in international application No. PCT/US2011/036097, dated Nov. 13, 2012.
Patent Cooperation Treaty, Written Opinion of the International Searching Authority with International Search Report in Application No. PCT/US2012/064489, dated Jan. 25, 2013.
Danish Patent and Trademark Office, Singapore Written Opinion, in Application No. 201108308-6, dated Dec. 6, 2012.
Danish Patent and Trademark Office, Singapore Search Report, in Application No. 201108308-6, dated Dec. 12, 2012.
Tao, Ran et al., Condensationand Polymerization of Supersaturated Monomer Vapor, ACS Publications, 2012 American Chemical Society, ex.doi.org/10.1021/la303462q/Langmuir 2012, 28, 16580-16587.
State Intellectual Property Office of Teh People's Republic of China, Notification of First Office fiction in Application No. 201080029201.4, dated Mar. 37, 2013. (15 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/040380, dated Sep. 3, 2013. (13 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/040368, dated Oct. 21, 2013 (21 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/048709, dated Oct. 2, 2013. (7 pages).
Coclite A.M. et al., "On the relationship between the structure and the barrier performance of plasma deposited silicon dioxide-like films", Surface and Coatings Technology, Elsevier, Amsterdam, NL, vol. 204, No. 24, Sep. 15, 2010 (Sep. 15, 2010), pp. 4012-4017, XPO27113381, ISSN: 0257-8972 [retrieved on Jun. 16, 2010] abstract, p. 4014, right-hand column—p. 4015, figures 2, 3.
Brunet-Bruneau A. et al., "Microstructural characterization of ion assisted Sio2 thin films by visible and infrared ellipsometry", Journal of Vacuum Science and Technology: Part A, AVS/AIP, Melville, NY, US, vol. 16, No. 4, Jul. 1, 1998 (Jul. 1, 1998), pp. 2281-2286, XPO12004127, ISSN: 0734-2101, DOI: 10.1116/1.581341, p. 2283, right-hand column—p. 2284, left-hand column, figures 2, 4.
Sahagian, Khoren; Larner, Mikki; Kaplan, Stephen L., "Altering Biological Interfaces with Gas Plasma: Example Applications", Plasma Technology Systems, Belmont, CA, In SurFACTS in Biomaterials, Surfaces in Biomaterials Foundation, Summer 2013, 18(3), p. 1-5.
Daikyo Cyrystal Zenith Insert Needle Syringe System, West Delivering Innovative Services, West Pharmaceutical Services, Inc., 2010.
Daikyo Crystal Zenigh Syringes, West Pharmaceutical Services, Inc., www.WestPFSsolutions.com, #5659, 2011.
Zhang, Yongchao and Heller, Adam, Reduction of the Nonspecific Binding of a Target Antibody and of Its Enzyme-Labeled Detection Probe Enabling Electrochemical Immunoassay of Antibody through the 7 pg/mL-100 ng/mL (40 fM-400 pM) Range, Department of Chemical Engineering and Texas Materials Institute, University of Texas at Austin, Anal. Chem. 2005, 7, 7758-7762. (6 pages).
Principles and Applications of Liquid Scintillation Counting, LSC Concepts—Fundamentals of Liquid Scintillation Counting, National Diagnostics, 2004, pp. 1-15.
Chikkaveeraiah, Bhaskara V. and Rusling, Dr. James, Non Specific Binding (NSB) in Antigen-Antibody Assays, University of Connecticut, Spring 2007. (13 pages).
Sahagian, Khoren; Larner, Mikki; Kaplan, Stephen L, "Cold Gas Plasma in Surface Modification of Medical Plastics", Plasma Technology Systems, Belmont, CA, Publication pending. Presented at SPE Antec Medical Plastics Division, Apr. 23, 2013, Ohio.
Lipman, Melissa, "Jury Orders Becton to Pay $114M in Syringe Antitrust Case", © 2003-2013, Portfolio Media, Inc., Law360, New York (Sep. 20, 2013, 2:53 PM ET), http://www.law360.com/articles/474334/print?section=ip, [retrieved Sep. 23, 2013].
Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Birefringence, page last modified Sep. 18, 2013 at 11:39. [retrieved on Oct. 8, 2013]. (5 pages).
Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Confocal_microscopy, page last modified Aug. 28, 2013 at 11:12. [retrieved on Oct. 8, 2013]. (4 pages).
Wang, Jun et al., "Fluorocarbon thin film with superhydrophobic property prepared by pyrolysis of hexafluoropropylene oxide", Applied Surface Science, vol. 258, 2012, pp. 9782-9784 (4 pages).

(56) **References Cited**

OTHER PUBLICATIONS

Wang, Hong et al., "Ozone-Initiated Secondary Emission Rates of Aldehydes from Indoor surfaces in Four Homes", American Chemical Society, Environmental Science & Technology, vol. 40, No. 17, 2006, pp. 5263-5268 (6 pages).
Lewis, Hilton G. Pryce, et al., "HWCVD of Polymers: Commercialization and Scale-Up", Thin Solid Films 517, 2009, pp. 3551-3554.
Wolgemuth, Lonny, "Challenges With Prefilled Syringes: The Parylene Solution", Frederick Furness Publishing, www.ongrugdelivery.com, 2012, pp. 44-45.
History of Parylene (12 pages).
SCS Parylene HTX brochure, Stratamet Thin Film Corporation, Fremont, CA, 2012, retrieved from the Internet Feb. 13, 2013, http://www.stratametthinfilm.com/parylenes/htx. (2 pages).
SCS Parylene Properties, Specialty Coating Systems, Inc., Indianapolis, IN, 2011. (12 pages).
Werthheimer, M.R., Studies of the earliest stages of plasma-enhanced chemical vapor deposition of SiO2 on polymeric substrates, Thin Solid Films 382 (2001) 1-3, and references therein, United States Pharmacopeia 34. In General Chapters <1>, 2001.
Gibbins, Bruce and Warner, Lenna, The Role of Antimicrobial Silver Nanotechnology, Medical Device & Diagnostic Industry, Aug. 205, pp. 2-6.
MTI CVD Tube Furnace w Gas Delivery & Vacuum Pump, http://mtixtl.com/MiniCVDTubeFurnace2ChannelsGasVacuum-OTF-1200X-S50-2F.aspx (2 pages).
Lab-Built HFPO CVD Coater, HFPO Decomp to Give Thin Fluorocarbon Films, Applied Surface Science 2012 258 (24) 9782.
Technical Report No. 10, Journal of Parenteral Science and Technology, 42, Supplement 1988, Parenteral Formulation of Proteins and Peptides: Stability and Stabilizers, Parenteral Drug Association, 1988.
Technical Technical Report No. 12, Journal of Parenteral Science and Technology, 42, Supplement 1988, Siliconization of Parenteral Drug Packaging Components, Parenteral Drug Association, 1988.
European Patent Office, Communication under Rule 71(3) EPC, in Application No. 10 162 760.2-1353, dated Oct. 25, 2013. (366 pages).
Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Difluorocarbene, page last modified Feb. 20, 2012 at 14:41. [retrieved on Sep. 7, 2012]. (4 pages).
O'Shaughnessy, W.S., et al., "Initiated Chemical Vapor Deposition of a Siloxane Coating for Insulation of Neutral Probes", Thin Solid Films 517 (2008) 3612-3614. (3 pages).
Denler, et al., Investigations of SiOx-polymer "interphases" by glancing angle RBS with Li+ and Be+ ions, Nuclear Instruments and Methods in Physical Research B 208 (2003) 176-180, United States Pharmacopeia 34. In General chapters <1>, 2003.
PCT, Invitation to Pay Additional Fees and Annex to Form PCT/ISA/206 Communication relating to the results of the partial international search in International application No. PCT/US2013/071750, dated Feb. 14, 2014. (6 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/62247, dated Dec. 30, 2013. (13 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/043642, dated Dec. 5, 2013. (21 pages).
Japanese Patent Office, Notice of Reason(s) for Rejection in Patent application No. 2012-510983, dated Jan. 7, 2014. (6 pages).
Chinese Patent Office, Notification of the Second Office Action in Application No. 201080029199.0, dated Jan. 6, 2014. (26 pages).
Chinese Patent Office, Notification of the First Office Action in Application No. 201180023474.2, dated Dec. 23, 2013. (18 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/067852, dated Jan. 22, 2014. (9 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/064121, dated Mar. 24, 2014. (8 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/070325, dated Mar. 24, 2014. (16 pages).
Australian Government, IP Australia, Patent Examination Report No. 1, in Application No. 2010249031, dated Mar. 13, 2014. (4 pages).
Australian Government, IP Australia, Patent Examination Report No. 1, in Application No. 2013202893, dated Mar. 13, 2014. (4 pages).
European Patent Office, Communication pursuant to Article 93(3) EPC, in Application No. 11 731 554.9 dated April 15, 2014. (7 pages).
PCT, Notification Concerning Transmittal of International Preliminary Report on Patentability, in International application No. PCT/US2012/064489, dated May 22, 2014. (10 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2013/071750, dated Apr. 4, 2014. (13 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or Declaration, in International Application No. PCT/US2004/019884, dated May 23, 2014. (16 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2014/023813, dated May 22, 2014. (11 pages).
European Patent Office, Communication pursuant to Article 94(3) EPC, in Application No. 11 736 511.4, dated Mar. 28, 2014.
PCT, Notification Concerning Transmittal of International Preliminary Report on Patentability, in International application No. PCT/US2011/042387, dated Jan. 17, 2013. (7 pages).
State Intellectual Property Office of The People'Republic of China, Notification of the First Office Action, in Application No. 201180032145.4, dated Jan. 30, 2014. (16 pages).
PCT, Notification Concerning Transmittal of International Preliminary Report on Patentability, in International application No. PCT/US2011/044215, dated Jan. 31, 2013. (14 pages).
Da Silva Sobrinho A S et al., "Transparent barrier coatings on polyethylene terephthalate by single-and dual-frequency plasma-enhanced chemical vapor deposition", Journal of Vacuum Science and Technology; Part A, AVS/AIP, Melville, NY, US, vol. 16, No. 6, Nov. 1, 1998 (Nov. 1, 1998), pp. 3190-3198, XP01200471, ISSN: 0734-2101, DOI: 10.1116/1.581519 (9 pages).
State Intellectual Property Office of the People'S Republic of China, Notification of the Third Office Action, in Application No. 201080029201.4, dated Jul. 7, 2014 (15 pages).
PCT, Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, in International application No. PCT/US2014/029531, dated Jun. 20, 2014 (12 pages).
State Intellectual Property Office of the People's Republic of China, Notification of the Third Office Action, with translation, in Application No. 201080029199.0, dated Jun. 27, 2014 (19 pages).
Intellectual Property Office of Singapore, Invitation to Respond to Written Opinion, in Application No. 2012083077, dated Jun. 30, 2014 (12 pages).
PCT, Notification of Transmittal of International Preliminary Report on Patentability, in International application No. PCT/US13/40368, dated Jul. 16, 2014 (6 pages).
Australian Government, IP Australia, Patent Examination Report No. 1, in Application No. 2012318242, dated Apr. 30, 2014. (6 pages).
State Intellectual Property Office of the People'S Republic of China, Notification of the First Office Action, in Application No. 201180023461.5, dated May 21, 2014. (25 pages).

(56) **References Cited**

OTHER PUBLICATIONS

European Patent Office, Communication pursuant to Article 94(3) EPC, in Application No. 10162758.6 dated May 27, 2014. (7 pages).
Australian Government, IP Australia, Patent Examination Report No. 1, in Application No. 2011252925, dated Sep. 6, 2013 (3 pages).
PCT, Written Opinion of the International Preliminary Examining Authority, in International application No. PCT/USUS13/048709, dated Sep. 30, 2014 (4 pages).
PCT, Notification of Transmittal of the International Preliminary Report on Patentability, in International application No. PCT/USUS13/048709, dated Oct. 15, 2014 (7 pages).
PCT, Written Opinion of the International Preliminary Examining Authority, in International application No. PCT/USUS13/064121, dated Nov. 19, 2014 (8 pages).
PCT, Written Opinion of the International Preliminary Examining Authority, in International application No. PCT/USUS13/064121, dated Nov. 21, 2014 (7 pages).
Intellectual Property Corporation of Malaysia, Substantive Examintion Adverse Report (section 30(1)/30(2)), in Application No. PI 2011005486, dated Oct. 31, 2014 (3 pages).
Patent Office of the Russian Federation, Official Action, in Application No. 2011150499, dated Sep. 25, 2014 (4 pages).
Instituto Mexicano de la Propiedad Indutrial, Official Action, in Appilcation No. MX/a/2012/013129, dated Sep. 22, 2014 (5 pages).
Australian Government, Patent Examination Report No. 2 in Application No. 2010249031 dated Apr. 21, 2015.
Japanese Patent Office, Notice of Reasons for Refusal in application No. 2013-510276, dated Mar. 31, 2015.
Bose, Sagarika and Constable, Kevin, Advanced Delivery Devices, Design & Evaluation of a Polymer-Based Prefillable Syringe for Biopharmaceuticals With Improved Functionality & Performance, JR Automation Technologies, May 2015.
Hopwood J ED—CRC Press: "Plasma-assisted deposition", Aug. 17, 1997 (Aug. 17, 1997), Handbook of Nanophase Materials, Chapter 6, pp. 141-197, XP008107730, ISBN: 978-0-8247-9469-9.
PCT, Written Opinion of the International Preliminary Examining Authority, International application No. PCT/SU2013/071752, dated May 6, 2015.
Hlobik, Plastic Pre-Fillable Syringe Systems (http://www.healthcarepackaging.com/package-type/Containers/plastic-prefillablesyringe-systems, Jun. 8, 2010).
PCT, Written Opinion of the International Preliminary Examining Authority, in International application No. PCT/US2013/071750, dated Jan. 20, 2015 (9 pages).
PCT, Written Opinion of the International Preliminary Examining Authority, in International application No. PCT/US2013/064121, dated Nov. 21, 2014 (7 pages).
Japanese Patent Office, Decision of Rejection in Application No. 2012-510983, dated Jan. 20, 2015 (4 pages).
Australian Government, IP Australia, Patent Examination Report No. 1, in Application No. 2010249033, dated Dec. 19, 2014 (7 pages).
Australian Government, IP Australia, Patent Examination Report No. 1, in Application No. 2011252925, dated Dec. 2, 2014 (3 pages).
State Intellectual Property Office of the People'S Republic of China, Notification of the Fourth Office Action in Application No. 201080029199.0, dated Mar. 18, 2015 (15 pages).
Reh, et al., Evaluation of stationary phases for 2-dimensional HPLC of Proteins—Validation of commercial RP-columns, Published by Elsevier B.V, 2000.
Japanese Patent Office, Notice of Reasons for Refusal, Patent Application No. 2013-510276, mailed Mar. 8, 2016 (15 pages).
Korean Patent Office, Office Action dated Jun. 21, 2016 in Patent Application No. 10-2011-7028713 (23 pages).

* cited by examiner

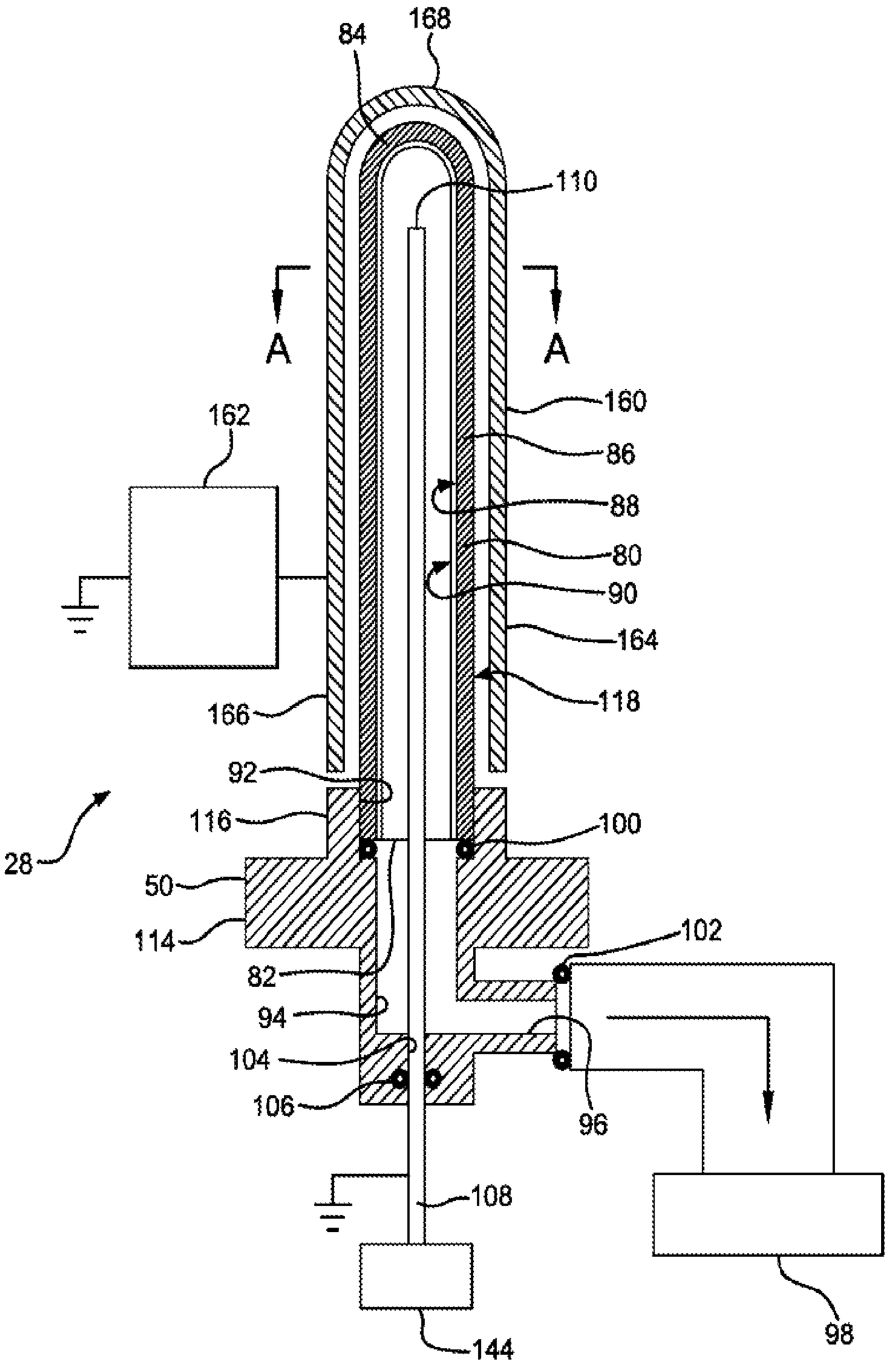
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FIG. 1

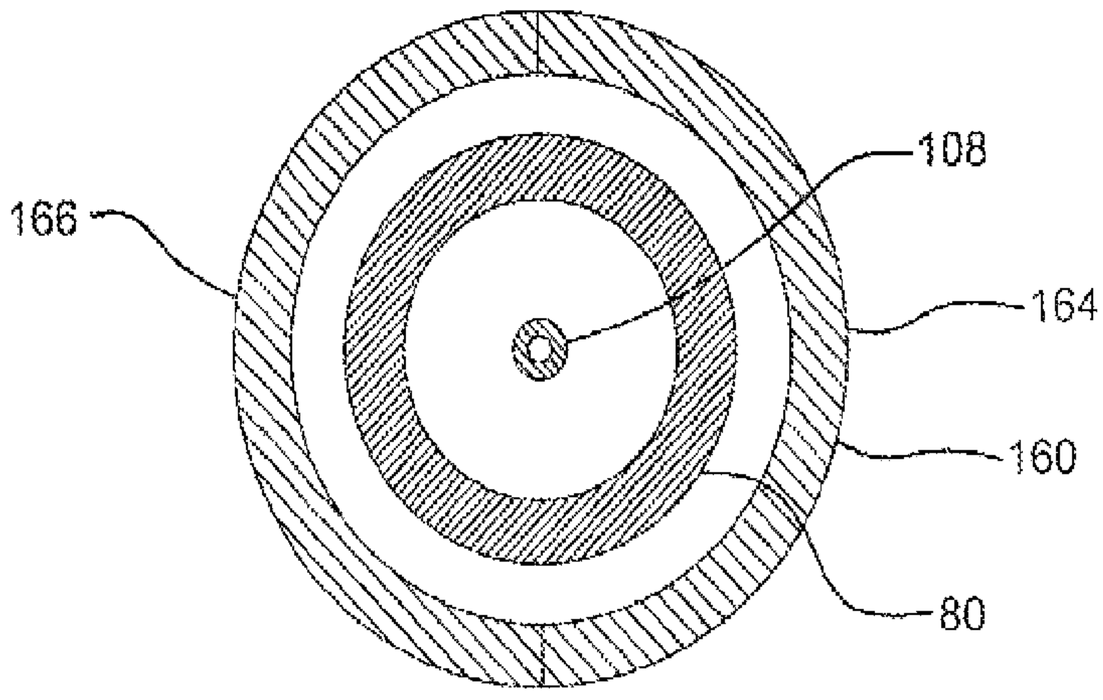

FIG. 2

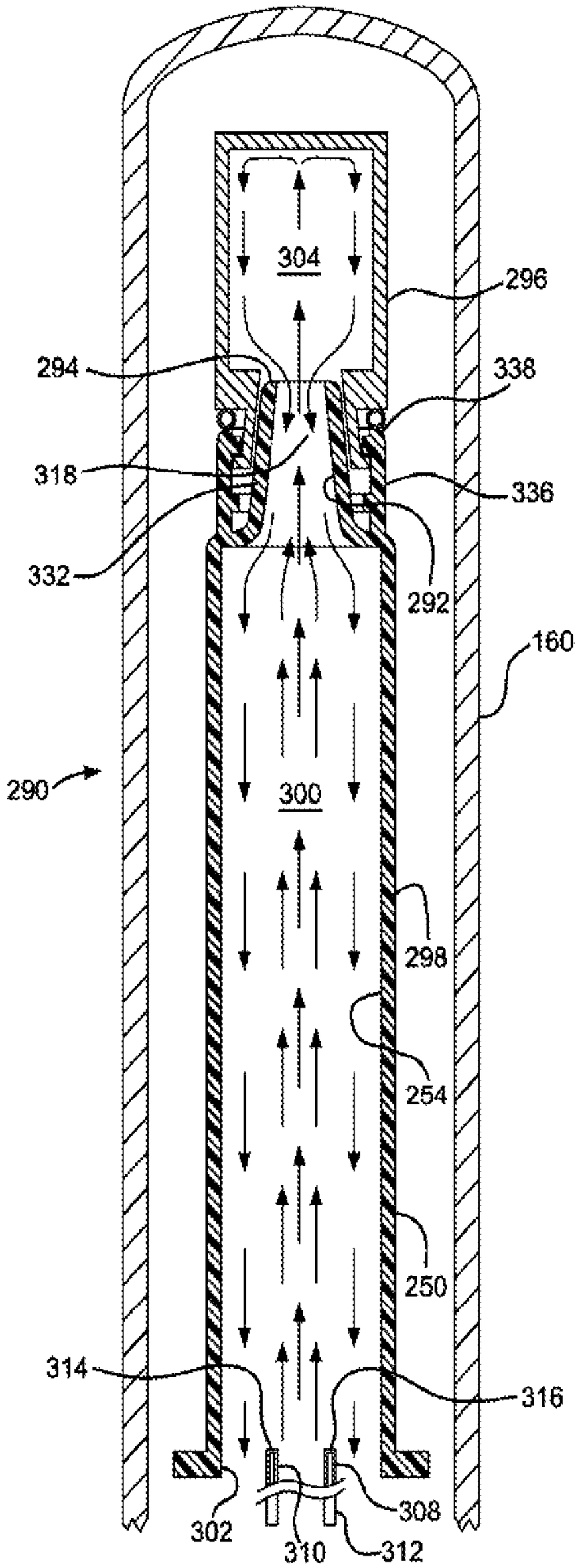
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FIG. 3

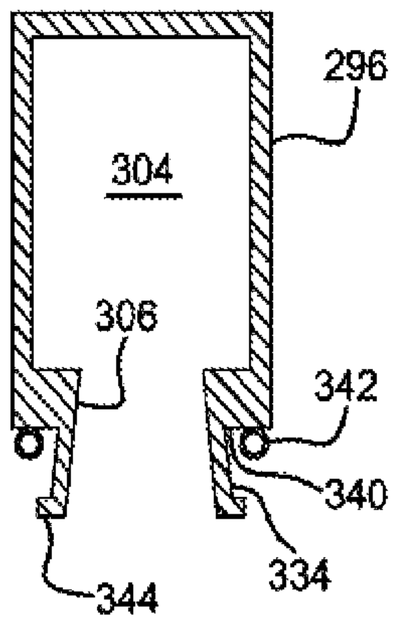
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FIG. 4

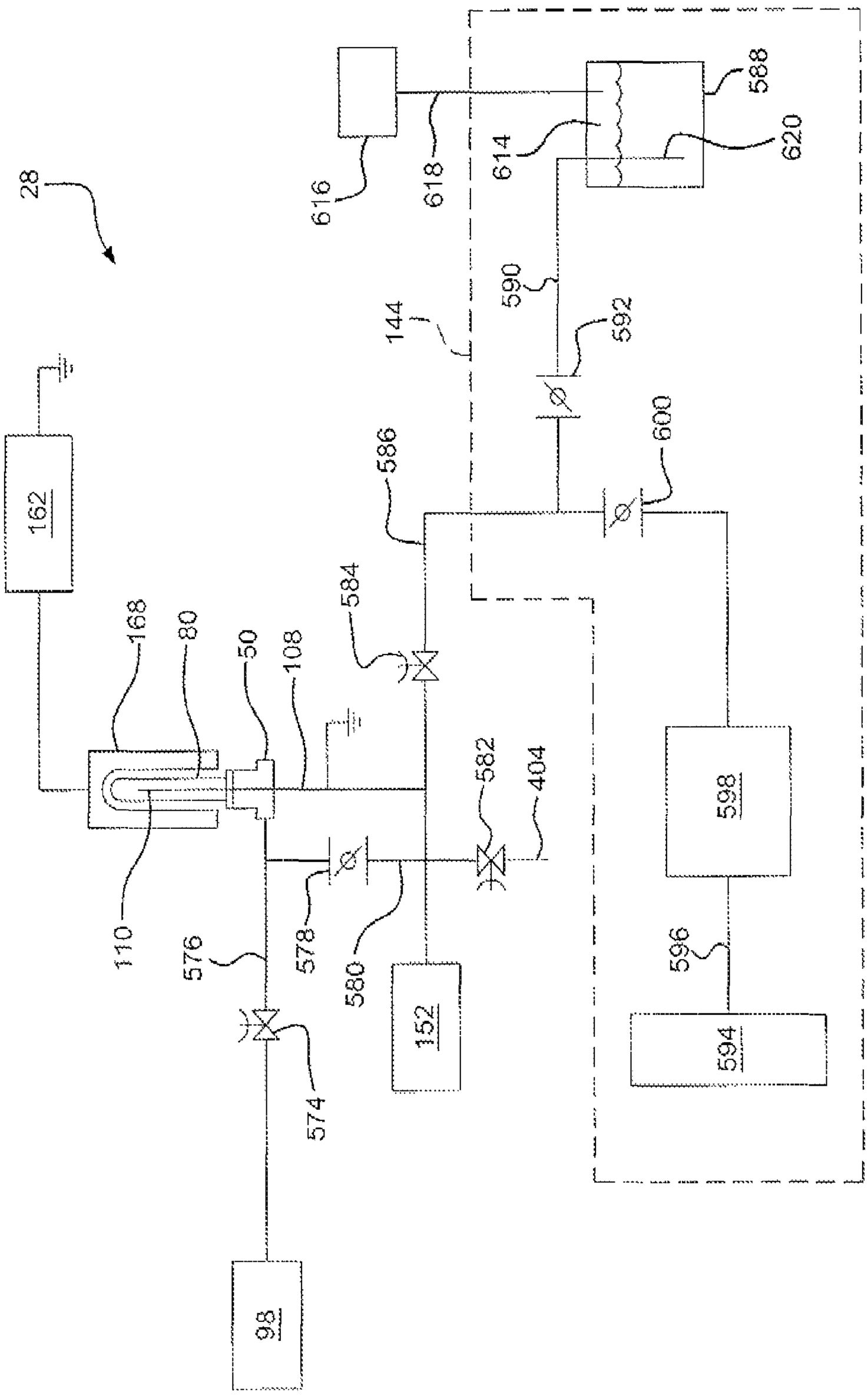
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FIG. 5

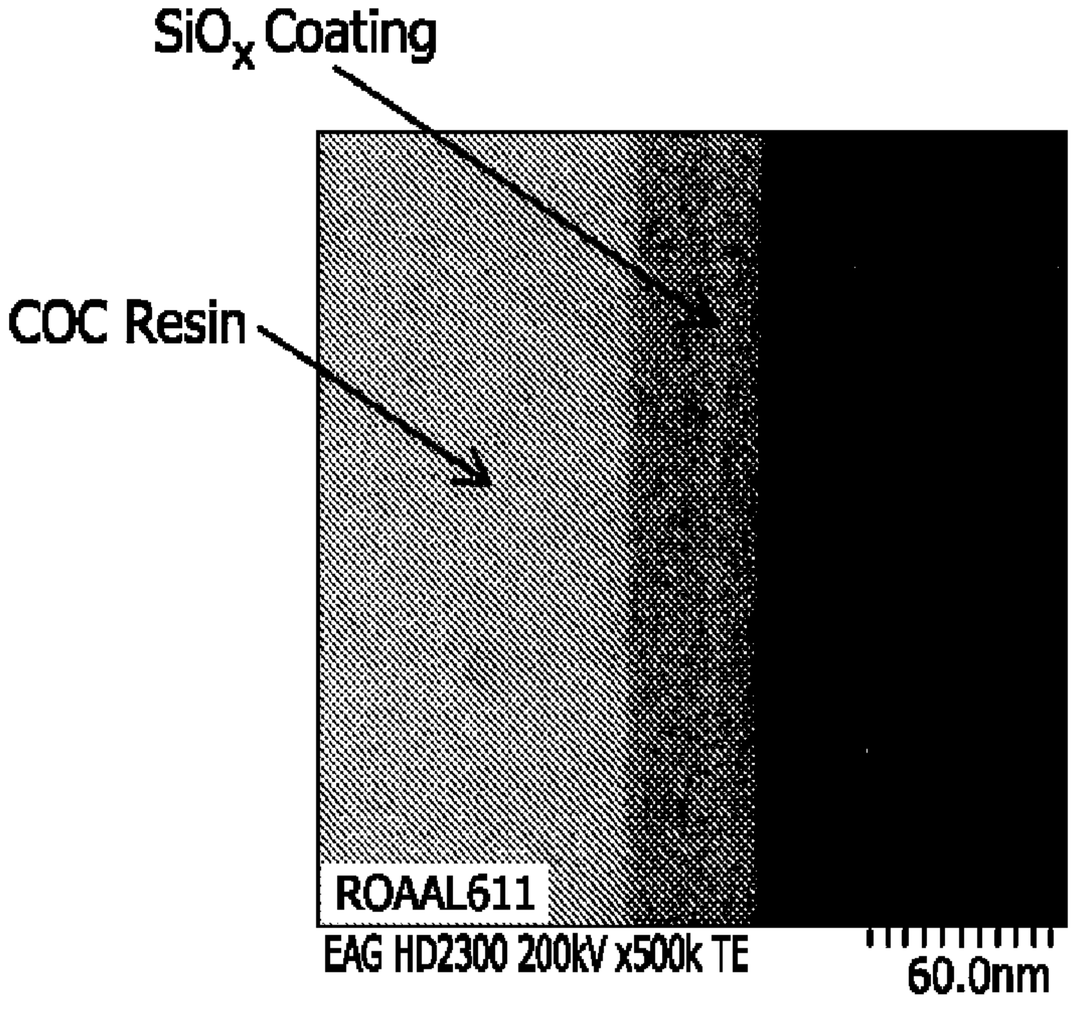
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FIG.6

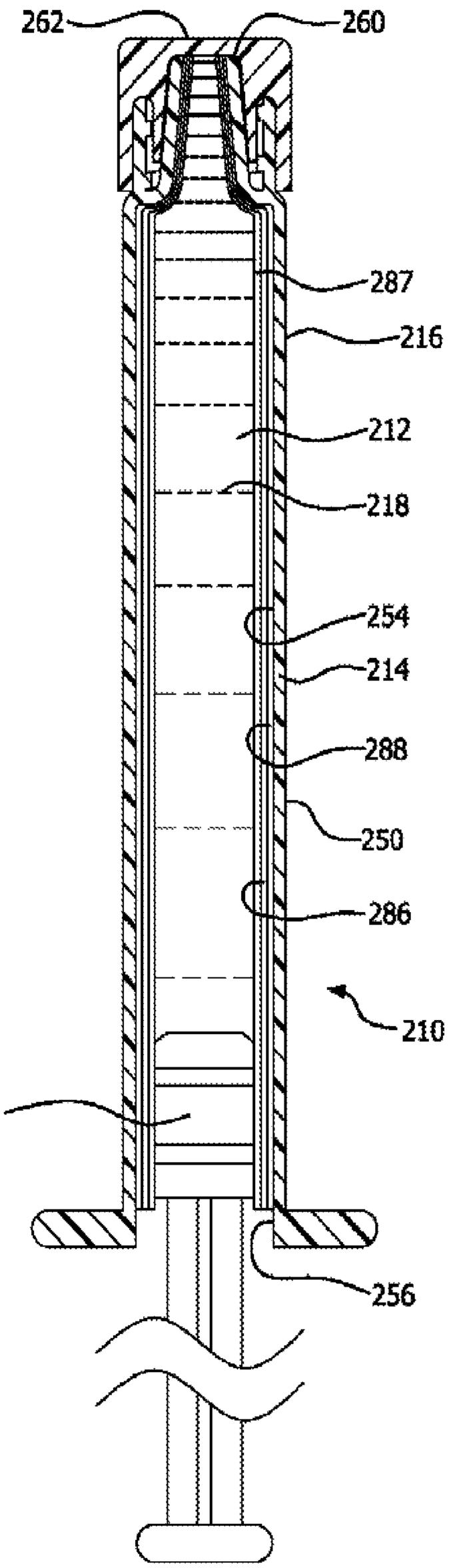


FIG. 7

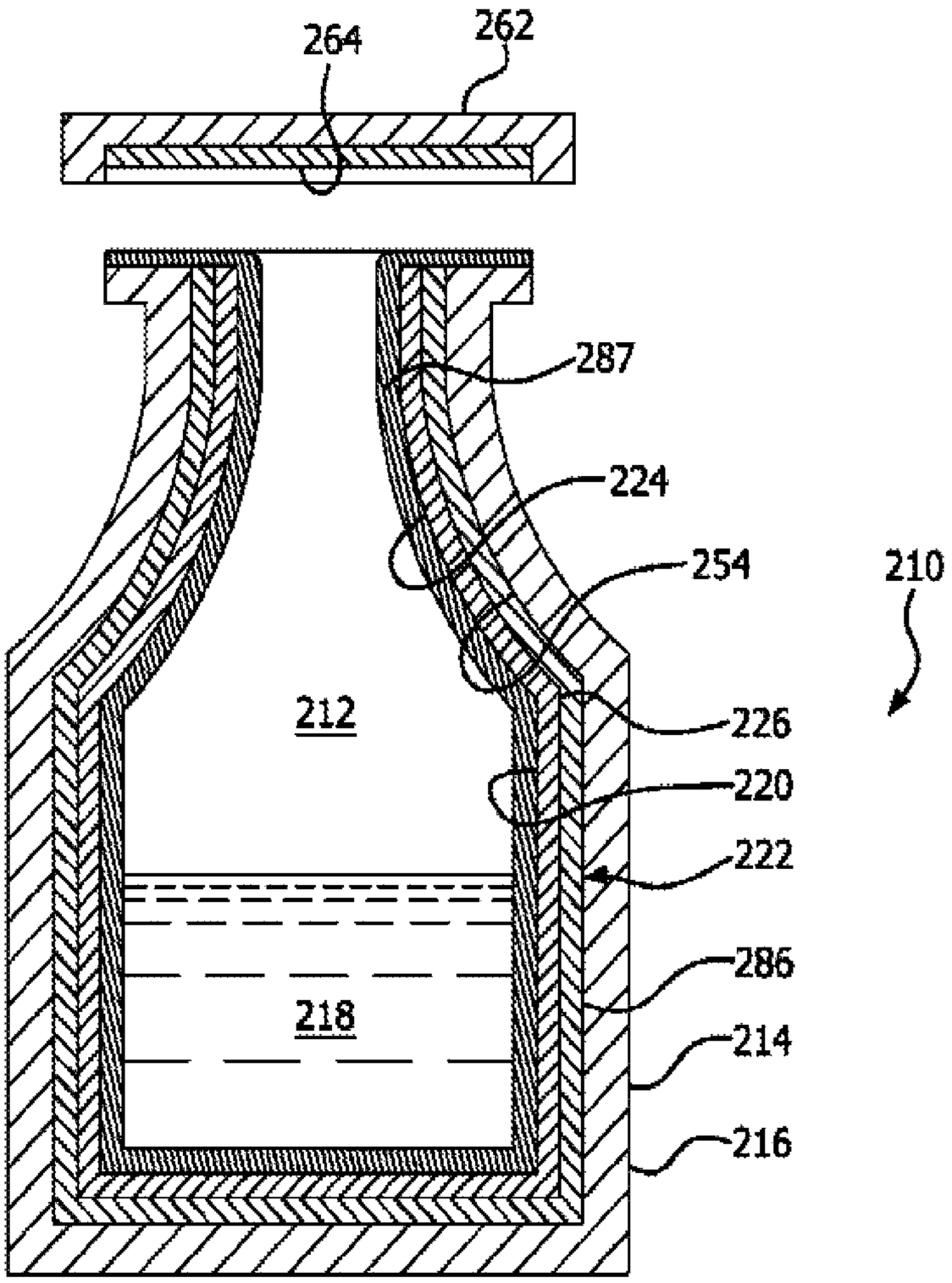

264
262
287
224
254
210
212
226
220
222
286
218
214
216

FIG. 8

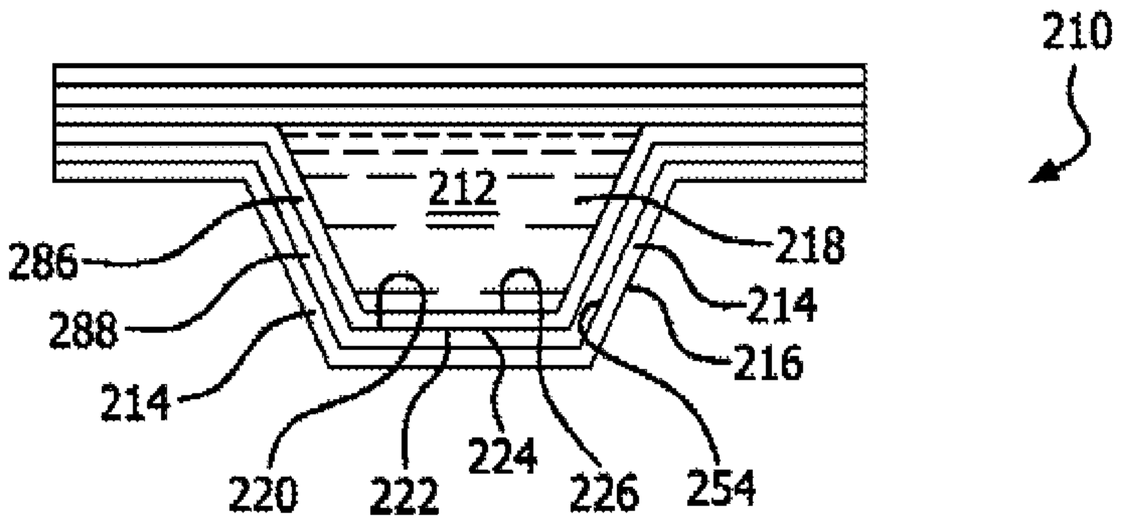

210
212
286
288
214
218
214
216
220
222
224
226
254

FIG. 9

SACCHARIDE PROTECTIVE COATING FOR PHARMACEUTICAL PACKAGE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Phase of International Application No. PCT/US2013/040380 filed May 9, 2013, which claims priority to U.S. Provisional Patent Application No, 61/644,961 filed May 9, 2012, which are incorporated herein by reference in their entirety.

The priority of U.S. Provisional Ser. No. 61/644,961, filed May 9, 2012, is claimed. That patent application is incorporated here by reference in its entirety.

U.S. Provisional Ser. Nos. 61/177,984 filed May 13, 2009; 61/222,727, filed Jul. 2, 2009; 61/213,904, filed Jul. 24, 2009; 61/234,505, filed Aug. 17, 2009; 61/261,321, filed Nov. 14, 2009; 61/263,289, filed Nov. 20, 2009; 61/285,813, filed Dec. 11, 2009; 61/298,159, filed Jan. 25, 2010; 61/299,888, filed Jan. 29, 2010; 61/318,197, filed Mar. 26, 2010; 61/333,625, filed May 11, 2010; 61/413,334, filed Nov. 12, 2010; Ser. No. 12/779,007, filed May 12, 2010, now U.S. Pat. No. 7,985,188; International Application PCT/US11/36097, filed May 11, 2011; and U.S. Ser. No. 61/558,885, filed Nov. 11, 2011; are all incorporated here by reference in their entirety.

Also incorporated by reference in their entirety are the following European patent applications: EP10162755.2 filed May 12, 2010; EP10162760.2 filed May 12, 2010; EP10162756.0 filed May 12, 2010; EP10162758.6 filed May 12, 2010; EP10162761.0 filed May 12, 2010; and EP10162757.8 filed May 12, 2010. These European patent applications describe apparatus, vessels, precursors, coatings or layers and methods (in particular coating methods and test methods for examining the coatings or layers) which can generally be used in performing the present invention, unless stated otherwise herein. They also describe SiO_x barrier coatings or layers to which reference is made herein.

FIELD OF THE INVENTION

The present invention relates to the technical field of coated surfaces, for example interior surfaces of pharmaceutical packages or other vessels for storing or other contact with fluids. Examples of suitable fluids include foods or biologically active compounds or body fluids, for example blood. The present invention also relates to a pharmaceutical package or other vessel and to a method for coating an inner or interior surface of a pharmaceutical package or other vessel. The present invention also relates more generally to medical devices, including devices other than packages or vessels, for example catheters.

The present disclosure also relates to improved methods for processing pharmaceutical packages or other vessels, for example multiple identical pharmaceutical packages or other vessels used for pharmaceutical preparation storage and delivery, venipuncture and other medical sample collection, and other purposes. Such pharmaceutical packages or other vessels are used in large numbers for these purposes, and must be relatively economical to manufacture and yet highly reliable in storage and use.

BACKGROUND OF THE INVENTION

One important consideration in manufacturing pharmaceutical packages or other vessels for storing or other contact with fluids, for example vials and pre-filled syringes,

is that the contents of the pharmaceutical package or other vessel desirably will have a substantial shelf life. During this shelf life, it is important to isolate the material filling the pharmaceutical package or other vessel from the vessel wall containing it, or from barrier layers or other functional layers applied to the pharmaceutical package or other vessel wall to avoid leaching material from the pharmaceutical package or other vessel wall, barrier layer, or other functional layers into the prefilled contents or vice versa.

Since many of these pharmaceutical packages or other vessels are inexpensive and used in large quantities, for certain applications it will be useful to reliably obtain the necessary shelf life without increasing the manufacturing cost to a prohibitive level.

For decades, most parenteral therapeutics have been delivered to end users in Type I medical grade borosilicate glass vessels such as vials or pre-filled syringes. The relatively strong, impermeable and inert surface of borosilicate glass has performed adequately for most drug products. However, the recent advent of costly, complex and sensitive biologics as well as such advanced delivery systems as auto injectors has exposed the physical and chemical shortcomings of glass pharmaceutical packages or other vessels, including possible contamination from metals, flaking, and breakage, among other problems. Moreover, glass contains several components which can leach out during storage and cause damage to the stored material. In more detail, borosilicate pharmaceutical packages or other vessels exhibit a number of drawbacks:

Glass is manufactured from sand containing a heterogeneous mixture of many elements (silicon, oxygen, boron, aluminum, sodium, calcium) with trace levels of other alkali and earth metals. Type I borosilicate glass consists of approximately 76% SiO_2, 10.5% B_2O_3, 5% Al_2O_3, 7% Na2O and 1.5% CaO and often contains trace metals such as iron, magnesium, zinc, copper and others. The heterogeneous nature of borosilicate glass creates a non-uniform surface chemistry at the molecular level. Glass forming processes used to create glass vessels expose some portions of the vessels to temperatures as great as 1200° C. Under such high temperatures alkali ions migrate to the local surface and form oxides. The presence of ions extracted from borosilicate glass devices may be involved in degradation, aggregation and denaturation of some biologics. Many proteins and other biologics must be lyophilized (freeze dried), because they are not sufficiently stable in solution in glass vials or syringes.

In glass syringes, silicon oil is typically used as a lubricant to allow the plunger to slide in the barrel. Silicon oil has been implicated in the precipitation of protein solutions such as insulin and some other biologics. Additionally, the silicon oil coating or layer is often non-uniform, resulting in syringe failures in the market.

Glass pharmaceutical packages or other vessels are prone to breakage or degradation during manufacture, filling operations, shipping and use, which means that glass particulates may enter the drug. The presence of glass particles has led to many FDA Warning Letters and to product recalls.

Glass-forming processes do not yield the tight dimensional tolerances required for some of the newer auto-injectors and delivery systems.

As a result, some companies have turned to plastic pharmaceutical packages or other vessels, which provide greater dimensional tolerance and less breakage than glass but lack its impermeability.

Although plastic is superior to glass with respect to breakage, dimensional tolerances and surface uniformity, its

use for primary pharmaceutical packaging remains limited due to the following shortcomings:

- Gas (oxygen) permeability: Plastic allows small molecule gases to permeate into (or out of) the device. The permeability of plastics to gases is significantly greater than that of glass and, in many cases (as with oxygen-sensitive drugs such as epinephrine), plastics have been unacceptable for that reason.
- Water vapor transmission: Plastics allow water vapors to pass through devices to a greater degree than glass. This can be detrimental to the shelf life of a solid (lyophilized) drug. Alternatively, a liquid product may lose water in an arid environment.
- Leachables and extractables: Plastic pharmaceutical packages or other vessels contain organic compounds that can leach out or be extracted into the drug product. These compounds can contaminate the drug and/or negatively impact the drug's stability.

Clearly, while plastic and glass pharmaceutical packages or other vessels each offer certain advantages in pharmaceutical primary packaging, neither is optimal for all drugs, biologics or other therapeutics. Thus, there is a desire for plastic pharmaceutical packages or other vessels, in particular plastic syringes, with gas and solute barrier properties which approach the properties of glass. Moreover, there is a need for plastic syringes with sufficient lubricity and/or protective properties and a lubricity and/or protective coating or layer which is compatible with the syringe contents.

There are additional considerations to be taken into account when manufacturing a prefilled syringe. Prefilled syringes are commonly prepared and sold so the syringe does not need to be filled before use, and can be disposed of after use. The syringe can be prefilled with saline solution, a dye for injection, or a pharmaceutically active preparation, for some examples.

Commonly, the prefilled syringe is capped at the distal end, as with a cap, and is closed at the proximal end by its drawn plunger. The prefilled syringe can be wrapped in a sterile package before use. To use the prefilled syringe, the packaging and cap are removed, optionally a hypodermic needle or another delivery conduit is attached to the distal end of the barrel, the delivery conduit or syringe is moved to a use position (such as by inserting the hypodermic needle into a patient's blood vessel or into apparatus to be rinsed with the contents of the syringe), and the plunger is advanced in the barrel to inject the contents of the barrel.

An important consideration regarding medical syringes is to ensure that the plunger can move at a constant speed and with a constant force when it is pressed into the barrel. A similar consideration applies to vessels such as pharmaceutical vials which have to be closed by a stopper, and to the stopper itself, and more generally to any surface which has to provide smooth operation of moving parts and/or be protectively coated.

A non-exhaustive list of documents of possible relevance includes U.S. Pat. Nos. 7,901,783; 6,068,884; 4,844,986; and 8067070 and U.S. Publ. Appl. Nos. 2008/0090039, 2011/0152820, 2006/0046006 and 2004/0267194. These documents are all incorporated by reference.

SUMMARY OF THE INVENTION

An aspect of the invention is a filled package comprising a vessel, a barrier coating and a protective coating on the vessel, and a fluid composition contained in the vessel. The calculated shelf life of the package is more than six months at a storage temperature of 4° C.

The vessel has a lumen defined at least in part by a wall. The wall has an interior surface facing the lumen and an outer surface.

The barrier coating comprises SiO_x, wherein x is from 1.5 to 2.9, from 2 to 1000 nm thick. The barrier coating of SiO_x has an interior surface facing the lumen and an outer surface facing the wall interior surface. The barrier coating is effective to reduce the ingress of atmospheric gas into the lumen compared to an vessel without a protective coating.

The protective coating comprises a protective coating or layer of a saccharide. The protective coating has an interior surface facing the lumen and an outer surface facing the interior surface of the barrier coating. The protective coating is effective to increase the calculated shelf life of the package (total Si/Si dissolution rate).

The fluid composition is contained in the lumen and has a pH between 5 and 9.

Another aspect of the invention is a filled package comprising a vessel, a saccharide protective coating on the vessel, and a fluid composition contained in the vessel.

The vessel has a lumen defined at least in part by a wall. The wall has an interior surface comprising glass facing the lumen and an outer surface.

The protective coating comprises a protective coating or layer of a saccharide. The protective coating has an interior surface facing the lumen and an outer surface facing the interior surface of the barrier coating. The protective coating is effective to decrease the Si dissolution rate of the glass interior surface.

The fluid composition is contained in the lumen and has a pH between 5 and 9.

Still another aspect of the invention is an article comprising a wall, a barrier coating, and a saccharide protective coating.

The wall has a surface.

The barrier coating comprises SiO_x, wherein x is from 1.5 to 2.9, from 2 to 1000 nm thick. The barrier coating of SiO_x has an interior surface facing the lumen and an outer surface facing the wall interior surface. The barrier coating is effective to reduce the ingress of atmospheric gas through the wall compared to an uncoated wall.

The protective coating of any embodiment is on the barrier coating and comprises a protective coating or layer of a saccharide. The protective coating is contemplated to be formed by binding a coupling agent to the barrier coating, then binding the saccharide to the binding agent, either directly or through intermediate agents. Alternatively, the coupling agent can first be bound to the saccharide, then the saccharide-binder combination can be bonded to the barrier coating or layer.

The rate of erosion of the protective coating, if directly contacted by a fluid composition having a pH at some point between 5 and 9, is less than the rate of erosion of the barrier coating, if directly contacted by the fluid composition.

Even another aspect of the invention is a vessel comprising a wall, a fluid contained in the vessel, a barrier coating, and a protective coating.

The wall is a thermoplastic wall having an interior surface enclosing a lumen.

The fluid is disposed in the lumen and has a pH greater than 5.

The barrier coating comprises SiO_x, in which x is between 1.5 and 2.9. The barrier coating is applied by PECVD. The barrier coating is positioned between the interior surface of the thermoplastic wall and the fluid, and supported by the thermoplastic wall. The barrier coating has the characteristic

of being subject to being measurably diminished in barrier improvement factor in less than six months as a result of attack by the fluid.

The protective coating comprises a saccharide. The protective coating is positioned between the barrier coating and the fluid. The protective coating is supported by the thermoplastic wall. The protective coating is effective to keep the barrier coating at least substantially undissolved as a result of attack by the fluid for a period of at least six months.

Also expressly contemplated is a syringe having a barrel, a plunger movable axially in the barrel, and an O-ring or other toroidal band interfacing between the plunger and the barrel. It is contemplated that the O-ring will function to reduce the "sticktion" force preventing initial movement of the plunger in the barrel by rolling along the plunger and barrel when the plunger is first subjected to an advancing force.

Other aspects of the invention will become apparent to a person of ordinary skill in the art after reviewing the present disclosure and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic sectional view of a vessel holder in a coating station according to an embodiment of the disclosure.

FIG. **2** is a section taken along section lines A-A of FIG. **1**.

FIG. **3** is a view similar to FIG. **1** of another embodiment for processing syringe barrels and other pharmaceutical packages or other vessels.

FIG. **4** is an enlarged detail view of the processing vessel of FIG. **3**.

FIG. **5** is a schematic view of an assembly for treating pharmaceutical packages or other vessels. The assembly is usable with the apparatus in any of the preceding figures.

FIG. **6** shows a TEM image of an SiO_2 barrier coating or layer which is coated on a COC substrate.

FIG. **7** is an assembly view of a prefilled syringe provided with a barrier layer, a protective coating or layer, and a lubricity layer and filled and closed to provide a pharmaceutical package.

FIG. **8** is a schematic view of a pharmaceutical package in the form of a vial provided with a barrier layer, a protective coating or layer, and optionally a lubricity layer.

FIG. **9** is a schematic view of a pharmaceutical package in the form of a blister package provided with a barrier layer and a protective coating or layer.

The following reference characters are used in the drawing figures:

28	coating station
50	Vessel holder
80	Vessel
82	Opening
84	Closed end
86	Wall
88	Inner or interior surface
90	Barrier layer
92	Vessel port
94	Vacuum duct
96	Vacuum port
98	Vacuum source
100	O-ring (of 92)
102	O-ring (of 96)
104	Gas inlet port
106	O-ring (of 100)
108	Probe (counter electrode)
110	Gas delivery port (of 108)
114	Housing (of 50 or 112)
116	Collar
118	Exterior surface (of 80)
144	PECVD gas source
152	Pressure gauge
160	Electrode
162	Power supply
164	Sidewall (of 160)
166	Sidewall (of 160)
168	Closed end (of 160)
210	Pharmaceutical package
212	Lumen
214	Wall
216	Outer surface
218	Fluid composition
220	Interior surface (of 288)
222	Outer surface (of 288)
224	Interior surface (of 286)
226	Outer surface (of 286)
250	Syringe barrel
254	Inner or interior surface (of 250)
256	Back end (of 250)
258	Plunger (of 252) (relatively sliding part)
260	Front end (of 250)
262	Cap
264	Inner or interior surface (of 262)
286	protective coating
287	Lubricity layer
288	Barrier layer
290	Apparatus for coating, for example, 250
292	Inner or interior surface (of 294)
294	Restricted opening (of 250)
296	Processing vessel
298	Outer surface (of 250)
300	Lumen (of 250)
302	Larger opening (of 250)
304	Processing vessel lumen
306	Processing vessel opening
308	Inner electrode
310	Interior passage (of 308)
312	Proximal end (of 308)
314	Distal end (of 308)
316	Distal opening (of 308)
318	Plasma
332	First fitting (male Luer taper)
334	Second fitting (female Luer taper)
336	Locking collar (of 332)
338	First abutment (of 332)
340	Second abutment (of 332)
342	O-ring
344	Dog
574	Main vacuum valve
576	Vacuum line
578	Manual bypass valve
580	Bypass line
582	Vent valve
584	Main reactant gas valve
586	Main reactant feed line
588	Organosilicon liquid reservoir
590	Organosilicon feed line (capillary)
592	Organosilicon shut-off valve
594	Oxygen tank
596	Oxygen feed line
598	Mass flow controller
600	Oxygen shut-off valve
614	Headspace
616	Pressure source
618	Pressure line
620	Capillary connection

DETAILED DESCRIPTION

The present invention will now be described more fully, with reference to the accompanying drawings, in which several embodiments are shown. This invention can, however, be embodied in many different forms and should not be

construed as limited to the embodiments set forth here. Rather, these embodiments are examples of the invention, which has the full scope indicated by the language of the claims. Like numbers refer to like or corresponding elements throughout. The following disclosure relates to all embodiments unless specifically limited to a certain embodiment.

Definition Section

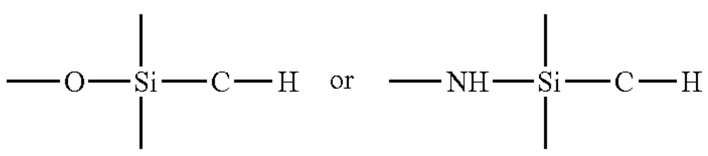
In the context of the present invention, the following definitions and abbreviations are used:

RF is radio frequency.

The term "at least" in the context of the present invention means "equal or more" than the integer following the term. The word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality unless indicated otherwise. Whenever a parameter range is indicated, it is intended to disclose the parameter values given as limits of the range and all values of the parameter falling within said range.

"First" and "second" or similar references to, for example, processing stations or processing devices refer to the minimum number of processing stations or devices that are present, but do not necessarily represent the order or total number of processing stations and devices. These terms do not limit the number of processing stations or the particular processing carried out at the respective stations.

For purposes of the present invention, an "organosilicon precursor" is a compound having at least one of the linkages:



which is a tetravalent silicon atom connected to an oxygen or nitrogen atom and an organic carbon atom (an organic carbon atom being a carbon atom bonded to at least one hydrogen atom). A volatile organosilicon precursor, defined as such a precursor that can be supplied as a vapor in a PECVD apparatus, is an optional organosilicon precursor. Optionally, the organosilicon precursor is selected from the group consisting of a linear siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, an alkyl trimethoxysilane, a linear silazane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, and a combination of any two or more of these precursors.

The feed amounts of PECVD precursors, gaseous reactant or process gases, and carrier gas are sometimes expressed in "standard volumes" in the specification and claims. The standard volume of a charge or other fixed amount of gas is the volume the fixed amount of the gas would occupy at a standard temperature and pressure (without regard to the actual temperature and pressure of delivery). Standard volumes can be measured using different units of volume, and still be within the scope of the present disclosure and claims. For example, the same fixed amount of gas could be expressed as the number of standard cubic centimeters, the number of standard cubic meters, or the number of standard cubic feet. Standard volumes can also be defined using different standard temperatures and pressures, and still be within the scope of the present disclosure and claims. For example, the standard temperature might be 0° C. and the standard pressure might be 760 Torr (as is conventional), or the standard temperature might be 20° C. and the standard pressure might be 1 Torr. But whatever standard is used in a given case, when comparing relative amounts of two or more different gases without specifying particular parameters, the same units of volume, standard temperature, and standard pressure are to be used relative to each gas, unless otherwise indicated.

The corresponding feed rates of PECVD precursors, gaseous reactant or process gases, and carrier gas are expressed in standard volumes per unit of time in the specification. For example, in the working examples the flow rates are expressed as standard cubic centimeters per minute, abbreviated as sccm. As with the other parameters, other units of time can be used, such as seconds or hours, but consistent parameters are to be used when comparing the flow rates of two or more gases, unless otherwise indicated.

A "vessel" in the context of the present invention can be any type of vessel with at least one opening and a wall defining an inner or interior surface. The substrate can be the inside wall of a vessel having a lumen. Though the invention is not necessarily limited to pharmaceutical packages or other vessels of a particular volume, pharmaceutical packages or other vessels are contemplated in which the lumen has a void volume of from 0.5 to 50 mL, optionally from 1 to 10 mL, optionally from 0.5 to 5 mL, optionally from 1 to 3 mL. The substrate surface can be part or all of the inner or interior surfaceinner or interior surface of a vessel having at least one opening and an inner or interior surfaceinner or interior surface.

The term "at least" in the context of the present invention means "equal or more" than the integer following the term. Thus, a vessel in the context of the present invention has one or more openings. One or two openings, like the openings of a sample tube (one opening) or a syringe barrel (two openings) are preferred. If the vessel has two openings, they can be of same or different size. If there is more than one opening, one opening can be used for the gas inlet for a PECVD coating method according to the present invention, while the other openings are either capped or open. A vessel according to the present invention can be a sample tube, for example for collecting or storing biological fluids like blood or urine, a syringe (or a part thereof, for example a syringe barrel) for storing or delivering a biologically active compound or composition, for example a medicament or pharmaceutical composition, a vial for storing biological materials or biologically active compounds or compositions, a pipe, for example a catheter for transporting biological materials or biologically active compounds or compositions, or a cuvette for holding fluids, for example for holding biological materials or biologically active compounds or compositions.

A vessel can be of any shape, a vessel having a substantially cylindrical wall adjacent to at least one of its open ends being preferred. Generally, the interior wall of the vessel is cylindrically shaped, like, for example in a sample tube or a syringe barrel. Sample tubes and syringes or their parts (for example syringe barrels) are contemplated.

A "lubricity and/or protective coating" according to the present invention is a coating or layer which has a lower frictional resistance than the uncoated surface, which is a lubricity layer, and/or protects an underlying surface or layer from a fluid composition contacting the layer, which is a protective coating or layer (as more extensively defined elsewhere in this specification). In other words, respecting a lubricity layer, it reduces the frictional resistance of the coated surface in comparison to a reference surface that is uncoated. The present lubricity and/or protective coatings are primarily defined as lubricity layers by their lower

frictional resistance than the uncoated surface and the process conditions providing lower frictional resistance than the uncoated surface.

"Frictional resistance" can be static frictional resistance and/or kinetic frictional resistance.

One of the optional embodiments of the present invention is a syringe part, for example a syringe barrel or plunger, coated with a lubricity and/or protective coating. In this contemplated embodiment, the relevant static frictional resistance in the context of the present invention is the breakout force as defined herein, and the relevant kinetic frictional resistance in the context of the present invention is the plunger sliding force as defined herein. For example, the plunger sliding force as defined and determined herein is suitable to determine the presence or absence and the lubricity and/or protective characteristics of a lubricity and/or protective coating or layer in the context of the present invention whenever the coating or layer is applied to any syringe or syringe part, for example to the inner wall of a syringe barrel. The breakout force is of particular relevance for evaluation of the coating or layer effect on a prefilled syringe, i.e. a syringe which is filled after coating and can be stored for some time, for example several months or even years, before the plunger is moved again (has to be "broken out").

The "plunger sliding force" (synonym to "glide force," "maintenance force", or Fm, also used in this description) in the context of the present invention is the force required to maintain movement of a plunger in a syringe barrel, for example during aspiration or dispense. It can advantageously be determined using the ISO 7886-1:1993 test described herein and known in the art. A synonym for "plunger sliding force" often used in the art is "plunger force" or "pushing force".

The "plunger breakout force" (synonym to "breakout force", "break loose force", "initiation force", Fi, also used in this description) in the context of the present invention is the initial force required to move the plunger in a syringe, for example in a prefilled syringe.

Both "plunger sliding force" and "plunger breakout force" and methods for their measurement are described in more detail in subsequent parts of this description. These two forces can be expressed in N, lbs or kg and all three units are used herein. These units correlate as follows: 1N=0.102 kg=0.2248 lbs (pounds).

Sliding force and breakout force are sometimes used herein to describe the forces required to advance a stopper or other closure into a pharmaceutical package or other vessel, such as a medical sample tube or a vial, to seat the stopper in a vessel to close the vessel. Its use is analogous to use in the context of a syringe and its plunger, and the measurement of these forces for a vessel and its closure are contemplated to be analogous to the measurement of these forces for a syringe, except that at least in most cases no liquid is ejected from a vessel when advancing the closure to a seated position.

"Slideably" means that the plunger, closure, or other removable part is permitted to slide in a syringe barrel or other vessel.

Coatings of SiO_x are deposited by plasma enhanced chemical vapor deposition (PECVD) or other chemical vapor deposition processes on the vessel of a pharmaceutical package, in particular a thermoplastic package, to serve as a barrier coating or layer preventing oxygen, carbon dioxide, or other gases from entering the vessel and/or to prevent leaching of the pharmaceutical material into or through the package wall. The inventors have found, however, that such barrier layers or coatings of SiO_x are eroded or dissolved by some fluid compositions, for example aqueous compositions having a pH above about 5. Since coatings applied by chemical vapor deposition can be very thin—tens to hundreds of nanometers thick—even a relatively slow rate of erosion can remove or reduce the effectiveness of the barrier layer in less time than the desired shelf life of a product package. This is particularly a problem for fluid pharmaceutical compositions, since many of them have a pH of roughly 7, or more broadly in the range of 5 to 9, similar to the pH of blood and other human or animal fluids. The higher the pH of the pharmaceutical preparation, the more quickly it erodes or dissolves the SiO_x coating.

The inventors have further found that certain protective coatings of a saccharide do not erode quickly when exposed to fluid compositions, and in fact erode or dissolve more slowly when the fluid compositions have higher pHs within the range of 5 to 9. For example, at pH 8, the dissolution rate of a protective coating made from a saccharide is quite slow. These protective coatings can therefore be used to cover a barrier layer of SiO_x, retaining the benefits of the barrier layer by protecting it from the fluid composition in the pharmaceutical package.

Three embodiments of the invention having many common features are those of FIGS. **7** TO **9**. Some of their common features are the following, indicated in many cases by common reference characters or names. The nature of the features of each embodiment can be as described later in the specification.

The pharmaceutical packages **210** of FIGS. **7** TO **9** each include a vessel, a fluid composition, a barrier coating, and a protective coating. The vessel **250** has a lumen **212** defined at least in part by a wall **214** made of thermoplastic material.

The wall **214** has an interior surface **254** facing the lumen **212** and an outer surface **216**.

The fluid composition **218** is contained in the lumen **212** and has a pH between 5 and 9.

The barrier coating **288** comprises or consists essentially of SiO_x, wherein x is from 1.5 to 2.9, from 2 to 1000 nm thick, the barrier coating **288** of SiO_x having an interior surface **220** facing the lumen **212** and an outer surface **222** facing the wall **214** interior surface **254**, the barrier coating **288** being effective to reduce the ingress of atmospheric gas into the lumen **212** compared to an uncoated vessel **250**. One suitable barrier composition is one where x is 2.3, for example.

The protective coating **286** is made of a saccharide. The protective coating **286** has an interior surface **224** facing the lumen **212** and an outer surface **226** facing the interior surface **220** of the barrier coating **288**.

The rate of erosion of the protective coating **286**, if directly contacted by the fluid composition **218**, is less than the rate of erosion of the barrier coating **288**, if directly contacted by the fluid composition **218**.

The protective coating **286** is effective to isolate the fluid composition **218** from the barrier coating **288**.

Optionally for any of the embodiments of FIGS. **7** TO **9**, at least a portion of the wall **214** of the vessel **250** comprises or consists essentially of a polymer, for example a polyolefin (for example a cyclic olefin polymer, a cyclic olefin copolymer, or polypropylene), a polyester, for example polyethylene terephthalate, a polycarbonate, or any combination or copolymer of any of these. Optionally for any of the embodiments of FIGS. **7** TO **9**, at least a portion of the wall **214** of the vessel **250** comprises or consists essentially of

glass, for example borosilicate glass. A combination of any two or more of the materials in this paragraph can also be used.

Optionally for the embodiments of FIG. **7**, the vessel **250** comprises a syringe barrel **250**.

Optionally for the embodiments of FIG. **8**, the vessel **250** comprises a vial that is an embodiment of the pharmaceutical package **210**.

Optionally for the embodiments of FIG. **9**, the vessel **250** comprises a blister package that is an embodiment of the pharmaceutical package **210287**.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the fluid composition **218** has a pH between 5 and 6, optionally between 6 and 7, optionally between 7 and 8, optionally between 8 and 9, optionally between 6.5 and 7.5, optionally between 7.5 and 8.5, optionally between 8.5 and 9.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the fluid composition **218** is a liquid at 20° C. and ambient pressure at sea level, which is defined as a pressure of 760 mm Hg.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the fluid composition **218** is an aqueous liquid.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the barrier coating **288** is from 4 nm to 500 nm thick, optionally from 7 nm to 400 nm thick, optionally from 10 nm to 300 nm thick, optionally from 20 nm to 200 nm thick, optionally from 30 nm to 100 nm thick.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the protective coating **286** comprises or consists essentially of a saccharide.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the protective coating **286** as applied is between 1000 and 5000 nm thick. The thickness does not need to be uniform throughout the vessel, and will typically vary from the preferred values in portions of a vessel.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the rate of erosion of the protective coating **286**, if directly contacted by a fluid composition **218** having a pH of 8, is less than 20%, optionally less than 15%, optionally less than 10%, optionally less than 7% , optionally from 5% to 20% , optionally 5% to 15% , optionally 5% to 10%, optionally 5% to 7%, of the rate of erosion of the barrier coating **288**, if directly contacted by the same fluid composition **218** under the same conditions.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the protective coating **286** is at least coextensive with the barrier coating **288**. The protective coating **286** alternatively can be less extensive than the barrier coating, as when the fluid composition does not contact or seldom is in contact with certain parts of the barrier coating absent the protective coating. The protective coating **286** alternatively can be more extensive than the barrier coating, as it can cover areas that are not provided with a barrier coating.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the pharmaceutical package **210** can have a shelf life, after the pharmaceutical package **210** is assembled, of at least one year, alternatively at least two years.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the shelf life is measured at 3° C., alternatively at 4° C. or higher, alternatively at 20° C. or higher, alternatively at 23° C., alternatively at 40° C.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the pH of the fluid composition **218** is between 5 and 6 and the thickness by TEM of the protective coating **286** is at least 80 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 6 and 7 and the thickness by TEM of the protective coating **286** is at least 80 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 7 and 8 and the thickness by TEM of the protective coating **286** is at least 80 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 8 and 9 and the thickness by TEM of the protective coating **286** is at least 80 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 5 and 6 and the thickness by TEM of the protective coating **286** is at least 150 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 6 and 7 and the thickness by TEM of the protective coating **286** is at least 150 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 7 and 8 and the thickness by TEM of the protective coating **286** is at least 150 nm at the end of the shelf life. Alternatively, the pH of the fluid composition **218** is between 8 and 9 and the thickness by TEM of the protective coating **286** is at least 150 nm at the end of the shelf life.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the fluid composition **218** removes the protective coating **286** at a rate of 1 nm or less of lubricity and/or protective coating thickness per 44 hours of contact with the fluid composition **218** (200 nm per year), alternatively 1 nm or less of lubricity and/or protective coating thickness per 88 hours of contact with the fluid composition **218** (100 nm per year), alternatively 1 nm or less of lubricity and/or protective coating thickness per 175 hours of contact with the fluid composition **218** (50 nm per year), alternatively 1 nm or less of lubricity and/or protective coating thickness per 250 hours of contact with the fluid composition **218** (35 nm per year), alternatively 1 nm or less of lubricity and/or protective coating thickness per 350 hours of contact with the fluid composition **218** (25 nm per year). The rate of removing the protective coating can be determined by TEM from samples exposed to the fluid composition for known periods.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the protective coating **286** is effective to provide a lower frictional resistance than the uncoated interior surface **254**. Preferably the frictional resistance is reduced by at least 25%, more preferably by at least 45%, even more preferably by at least 60% in comparison to the uncoated interior surface **254**. For example, the protective coating **286** preferably is effective to reduce the frictional resistance between a portion of the wall **214** contacted by the fluid composition **218** and a relatively sliding part **258** after the pharmaceutical package **210** is assembled. Preferably, the protective coating **286** is effective to reduce the frictional resistance between the wall **214** and a relatively sliding part **258** at least two years after the pharmaceutical package **210** is assembled.

Optionally for any of the embodiments of FIGS. **7** TO **9**, the fluid composition **218** comprises a member or a combination of two or more members selected from the group consisting of:

Inhalation Anesthetics
Aliflurane
Chloroform
Cyclopropane
Desflurane (Suprane)
Diethyl Ether
Enflurane (Ethrane)
Ethyl Chloride
Ethylene
Halothane (Fluothane)
Isoflurane (Forane, Isoflo)
Isopropenyl vinyl ether

Methoxyflurane
methoxyflurane,
Methoxypropane
Nitrous Oxide
Roflurane
Sevoflurane (Sevorane, Ultane, Sevoflo)
Teflurane
Trichloroethylene
Vinyl Ether
Xenon
Injectable Drugs
Ablavar (Gadofosveset Trisodium Injection)
Abarelix Depot
Abobotulinumtoxin A Injection (Dysport)
ABT-263
ABT-869
ABX-EFG
Accretropin (Somatropin Injection)
Acetadote (Acetylcysteine Injection)
Acetazolamide Injection (Acetazolamide Injection)
Acetylcysteine Injection (Acetadote)
Actemra (Tocilizumab Injection)
Acthrel (Corticorelin Ovine Triflutate for Injection)
Actummune
Activase
Acyclovir for Injection (Zovirax Injection)
Adacel
Adalimumab
Adenoscan (Adenosine Injection)
Adenosine Injection (Adenoscan)
Adrenaclick
AdreView (lobenguane 1123 Injection for Intravenous Use)
Afluria
Ak-Fluor (Fluorescein Injection)
Aldurazyme (Laronidase)
Alglucerase Injection (Ceredase)
Alkeran Injection (Melphalan Hcl Injection)
Allopurinol Sodium for Injection (Aloprim)
Aloprim (Allopurinol Sodium for Injection)
Alprostadil
Alsuma (Sumatriptan Injection)
ALTU-238
Amino Acid Injections
Aminosyn
Apidra
Apremilast
Alprostadil Dual Chamber System for Injection (Caverject Impulse)
AMG 009
AMG 076
AMG 102
AMG 108
AMG 114
AMG 162
AMG 220
AMG 221
AMG 222
AMG 223
AMG 317
AMG 379
AMG 386
AMG 403
AMG 477
AMG 479
AMG 517
AMG 531
AMG 557
AMG 623
AMG 655
AMG 706
AMG 714
AMG 745
AMG 785
AMG 811
AMG 827
AMG 837
AMG 853
AMG 951
Amiodarone HCl Injection (Amiodarone HCl Injection)
Amobarbital Sodium Injection (Amytal Sodium)
Amytal Sodium (Amobarbital Sodium Injection)
Anakinra
Anti-Abeta
Anti-Beta7
Anti-Beta20
Anti-CD4
Anti-CD20
Anti-CD40
Anti-IFNalpha
Anti-IL13
Anti-OX40L
Anti-oxLDS
Anti-NGF
Anti-NRP1
Arixtra
Amphadase (Hyaluronidase Inj)
Ammonul (Sodium Phenylacetate and Sodium Benzoate Injection)
Anaprox
Anzemet Injection (Dolasetron Mesylate Injection)
Apidra (Insulin Glulisine [rDNA origin] Inj)
Apomab
Aranesp (darbepoetin alfa)
Argatroban (Argatroban Injection)
Arginine Hydrochloride Injection (R-Gene 10
Aristocort
Aristospan
Arsenic Trioxide Injection (Trisenox)
Articane HCl and Epinephrine Injection (Septocaine)
Arzerra (Ofatumumab Injection)
Asclera (Polidocanol Injection)
Ataluren
Ataluren-DMD
Atenolol Inj (Tenormin I.V. Injection)
Atracurium Besylate Injection (Atracurium Besylate Injection)
Avastin
Azactam Injection (Aztreonam Injection)
Azithromycin (Zithromax Injection)
Aztreonam Injection (Azactam Injection)
Baclofen Injection (Lioresal Intrathecal)
Bacteriostatic Water (Bacteriostatic Water for Injection)
Baclofen Injection (Lioresal Intrathecal)
Bal in Oil Ampules (Dimercarprol Injection)
BayHepB
BayTet
Benadryl
Bendamustine Hydrochloride Injection (Treanda)
Benztropine Mesylate Injection (Cogentin)
Betamethasone Injectable Suspension (Celestone Soluspan)
Bexxar
Bicillin C-R 900/300 (Penicillin G Benzathine and Penicillin G Procaine Injection)
Blenoxane (Bleomycin Sulfate Injection)

Bleomycin Sulfate Injection (Blenoxane)
Boniva Injection (Ibandronate Sodium Injection)
Botox Cosmetic (OnabotulinumtoxinA for Injection)
BR3-FC
Bravelle (Urofollitropin Injection)
Bretylium (Bretylium Tosylate Injection)
Brevital Sodium (Methohexital Sodium for Injection)
Brethine
Briobacept
BTT-1023
Bupivacaine HCl
Byetta
Ca-DTPA (Pentetate Calcium Trisodium Inj)
Cabazitaxel Injection (Jevtana)
Caffeine Alkaloid (Caffeine and Sodium Benzoate Injection)
Calcijex Injection (Calcitrol)
Calcitrol (Calcijex Injection)
Calcium Chloride (Calcium Chloride Injection 10%)
Calcium Disodium Versenate (Edetate Calcium Disodium Injection)
Campath (Altemtuzumab)
Camptosar Injection (Irinotecan Hydrochloride)
Canakinumab Injection (Ilaris)
Capastat Sulfate (Capreomycin for Injection)
Capreomycin for Injection (Capastat Sulfate)
Cardiolite (Prep kit for Technetium Tc99 Sestamibi for Injection)
Carticel
Cathflo
Cefazolin and Dextrose for Injection (Cefazolin Injection)
Cefepime Hydrochloride
Cefotaxime
Ceftriaxone
Cerezyme
Carnitor Injection
Caverject
Celestone Soluspan
Celsior
Cerebyx (Fosphenytoin Sodium Injection)
Ceredase (Alglucerase Injection)
Ceretec (Technetium Tc99m Exametazime Injection)
Certolizumab
CF-101
Chloramphenicol Sodium Succinate (Chloramphenicol Sodium Succinate Injection)
Chloramphenicol Sodium Succinate Injection (Chloramphenicol Sodium Succinate)
Cholestagel (Colesevelam HCL)
Choriogonadotropin Alfa Injection (Ovidrel)
Cimzia
Cisplatin (Cisplatin Injection)
Clolar (Clofarabine Injection)
Clomiphine Citrate
Clonidine Injection (Duraclon)
Cogentin (Benztropine Mesylate Injection)
Colistimethate Injection (Coly-Mycin M)
Coly-Mycin M (Colistimethate Injection)
Compath
Conivaptan Hcl Injection (Vaprisol)
Conjugated Estrogens for Injection (Premarin Injection)
Copaxone
Corticorelin Ovine Triflutate for Injection (Acthrel)
Corvert (Ibutilide Fumarate Injection)
Cubicin (Daptomycin Injection)
CF-101
Cyanokit (Hydroxocobalamin for Injection)
Cytarabine Liposome Injection (DepoCyt)
Cyanocobalamin
Cytovene (ganciclovir)
D.H.E. 45
Dacetuzumab
Dacogen (Decitabine Injection)
Dalteparin
Dantrium IV (Dantrolene Sodium for Injection)
Dantrolene Sodium for Injection (Dantrium IV)
Daptomycin Injection (Cubicin)
Darbepoietin Alfa
DDAVP Injection (Desmopressin Acetate Injection)
Decavax
Decitabine Injection (Dacogen)
Dehydrated Alcohol (Dehydrated Alcohol Injection)
Denosumab Injection (Prolia)
Delatestryl
Delestrogen
Delteparin Sodium
Depacon (Valproate Sodium Injection)
Depo Medrol (Methylprednisolone Acetate Injectable Suspension)
DepoCyt (Cytarabine Liposome Injection)
DepoDur (Morphine Sulfate XR Liposome Injection)
Desmopressin Acetate Injection (DDAVP Injection)
Depo-Estradiol
Depo-Provera 104 mg/ml
Depo-Provera 150 mg/ml
Depo-Testosterone
Dexrazoxane for Injection, Intravenous Infusion Only (Totect)
Dextrose/Electrolytes
Dextrose and Sodium Chloride Inj (Dextrose 5% in 0.9% Sodium Chloride)
Dextrose
Diazepam Injection (Diazepam Injection)
Digoxin Injection (Lanoxin Injection)
Dilaudid-HP (Hydromorphone Hydrochloride Injection)
Dimercarprol Injection (Bal in Oil Ampules)
Diphenhydramine Injection (Benadryl Injection)
Dipyridamole Injection (Dipyridamole Injection)
DMOAD
Docetaxel for Injection (Taxotere)
Dolasetron Mesylate Injection (Anzemet Injection)
Doribax (Doripenem for Injection)
Doripenem for Injection (Doribax)
Doxercalciferol Injection (Hectorol Injection)
Doxil (Doxorubicin Hcl Liposome Injection)
Doxorubicin Hcl Liposome Injection (Doxil)
Duraclon (Clonidine Injection)
Duramorph (Morphine Injection)
Dysport (Abobotulinumtoxin A Injection)
Ecallantide Injection (Kalbitor)
EC-Naprosyn (naproxen)
Edetate Calcium Disodium Injection (Calcium Disodium Versenate)
Edex (Alprostadil for Injection)
Engerix
Edrophonium Injection (Enlon)
Eliglustat Tartate
Eloxatin (Oxaliplatin Injection)
Emend Injection (Fosaprepitant Dimeglumine Injection)
Enalaprilat Injection (Enalaprilat Injection)
Enlon (Edrophonium Injection)
Enoxaparin Sodium Injection (Lovenox)
Eovist (Gadoxetate Disodium Injection)
Enbrel (etanercept)
Enoxaparin

Epicel
Epinepherine
Epipen
Epipen Jr.
Epratuzumab
Erbitux
Ertapenem Injection (Invanz)
Erythropoieten
Essential Amino Acid Injection (Nephramine)
Estradiol Cypionate
Estradiol Valerate
Etanercept
Exenatide Injection (Byetta)
Evlotra
Fabrazyme (Adalsidase beta)
Famotidine Injection
FDG (Fludeoxyglucose F 18 Injection)
Feraheme (Ferumoxytol Injection)
Feridex I.V. (Ferumoxides Injectable Solution)
Fertinex
Ferumoxides Injectable Solution (Feridex I.V.)
Ferumoxytol Injection (Feraheme)
Flagyl Injection (Metronidazole Injection)
Fluarix
Fludara (Fludarabine Phosphate)
Fludeoxyglucose F 18 Injection (FDG)
Fluorescein Injection (Ak-Fluor)
Follistim AQ Cartridge (Follitropin Beta Injection)
Follitropin Alfa Injection (Gonal-f RFF)
Follitropin Beta Injection (Follistim AQ Cartridge)
Folotyn (Pralatrexate Solution for Intravenous Injection)
Fondaparinux
Forteo (Teriparatide (rDNA origin) Injection)
Fostamatinib
Fosaprepitant Dimeglumine Injection (Emend Injection)
Foscarnet Sodium Injection (Foscavir)
Foscavir (Foscarnet Sodium Injection)
Fosphenytoin Sodium Injection (Cerebyx)
Fospropofol Disodium Injection (Lusedra)
Fragmin
Fuzeon (enfuvirtide)
GA101
Gadobenate Dimeglumine Injection (Multihance)
Gadofosveset Trisodium Injection (Ablavar)
Gadoteridol Injection Solution (ProHance)
Gadoversetamide Injection (OptiMARK)
Gadoxetate Disodium Injection (Eovist)
Ganirelix (Ganirelix Acetate Injection)
Gardasil
GC1008
GDFD
Gemtuzumab Ozogamicin for Injection (Mylotarg)
Genotropin
Gentamicin Injection
GENZ-112638
Golimumab Injection (Simponi Injection)
Gonal-f RFF (Follitropin Alfa Injection)
Granisetron Hydrochloride (Kytril Injection)
Gentamicin Sulfate
Glatiramer Acetate
Glucagen
Glucagon
HAE1
Haldol (Haloperidol Injection)
Havrix
Hectorol Injection (Doxercalciferol Injection)
Hedgehog Pathway Inhibitor
Heparin
Herceptin
hG-CSF
Humalog
Human Growth Hormone
Humatrope
HuMax
Humegon
Humira
Humulin
Ibandronate Sodium Injection (Boniva Injection)
Ibuprofen Lysine Injection (NeoProfen)
Ibutilide Fumarate Injection (Corvert)
Idamycin PFS (Idarubicin Hydrochloride Injection)
Idarubicin Hydrochloride Injection (Idamycin PFS)
Ilaris (Canakinumab Injection)
Imipenem and Cilastatin for Injection (Primaxin I.V.)
Imitrex
Incobotulinumtoxin A for Injection (Xeomin)
Increlex (Mecasermin [rDNA origin] Injection)
Indocin IV (Indomethacin Inj)
Indomethacin Inj (Indocin IV)
Infanrix
Innohep
Insulin
Insulin Aspart [rDNA origin] Inj (NovoLog)
Insulin Glargine [rDNA origin] Injection (Lantus)
Insulin Glulisine [rDNA origin] Inj (Apidra)
Interferon alfa-2b, Recombinant for Injection (Intron A)
Intron A (Interferon alfa-2b, Recombinant for Injection)
Invanz (Ertapenem Injection)
Invega Sustenna (Paliperidone Palmitate Extended-Release Injectable Suspension)
Invirase (saquinavir mesylate)
Iobenguane 1123 Injection for Intravenous Use (AdreView)
Iopromide Injection (Ultravist)
Ioversol Injection (Optiray Injection)
Iplex (Mecasermin Rinfabate [rDNA origin] Injection)
Iprivask
Irinotecan Hydrochloride (Camptosar Injection)
Iron Sucrose Injection (Venofer)
Istodax (Romidepsin for Injection)
Itraconazole Injection (Sporanox Injection)
Jevtana (Cabazitaxel Injection)
Jonexa
Kalbitor (Ecallantide Injection)
KCL in D5NS (Potassium Chloride in 5% Dextrose and Sodium Chloride Injection)
KCL in D5W
KCL in NS
Kenalog 10 Injection (Triamcinolone Acetonide Injectable Suspension)
Kepivance (Palifermin)
Keppra Injection (Levetiracetam)
Keratinocyte
KFG
Kinase Inhibitor
Kineret (Anakinra)
Kinlytic (Urokinase Injection)
Kinrix
Klonopin (clonazepam)
Kytril Injection (Granisetron Hydrochloride)
lacosamide Tablet and Injection (Vimpat)
Lactated Ringer's
Lanoxin Injection (Digoxin Injection)
Lansoprazole for Injection (Prevacid I.V.)
Lantus

Leucovorin Calcium (Leucovorin Calcium Injection)
Lente (L)
Leptin
Levemir
Leukine Sargramostim
Leuprolide Acetate
Levothyroxine
Levetiracetam (Keppra Injection)
Lovenox
Levocarnitine Injection (Carnitor Injection)
Lexiscan (Regadenoson Injection)
Lioresal Intrathecal (Baclofen Injection)
Liraglutide [rDNA] Injection (Victoza)
Lovenox (Enoxaparin Sodium Injection)
Lucentis (Ranibizumab Injection)
Lumizyme
Lupron (Leuprolide Acetate Injection)
Lusedra (Fospropofol Disodium Injection)
Maci
Magnesium Sulfate (Magnesium Sulfate Injection)
Mannitol Injection (Mannitol IV)
Marcaine (Bupivacaine Hydrochloride and Epinephrine Injection)
Maxipime (Cefepime Hydrochloride for Injection)
MDP Multidose Kit of Technetium Injection (Technetium Tc99m Medronate Injection)
Mecasermin [rDNA origin] Injection (Increlex)
Mecasermin Rinfabate [rDNA origin] Injection (Iplex)
Melphalan Hcl Injection (Alkeran Injection)
Methotrexate
Menactra
Menopur (Menotropins Injection)
Menotropins for Injection (Repronex)
Methohexital Sodium for Injection (Brevital Sodium)
Methyldopate Hydrochloride Injection, Solution (Methyldopate Hcl)
Methylene Blue (Methylene Blue Injection)
Methylprednisolone Acetate Injectable Suspension (Depo Medrol)
MetMab
Metoclopramide Injection (Reglan Injection)
Metrodin (Urofollitropin for Injection)
Metronidazole Injection (Flagyl Injection)
Miacalcin
Midazolam (Midazolam Injection)
Mimpara (Cinacalet)
Minocin Injection (Minocycline Inj)
Minocycline Inj (Minocin Injection)
Mipomersen
Mitoxantrone for Injection Concentrate (Novantrone)
Morphine Injection (Duramorph)
Morphine Sulfate XR Liposome Injection (DepoDur)
Morrhuate Sodium (Morrhuate Sodium Injection)
Motesanib
Mozobil (Plerixafor Injection)
Multihance (Gadobenate Dimeglumine Injection)
Multiple Electrolytes and Dextrose Injection
Multiple Electrolytes Injection
Mylotarg (Gemtuzumab Ozogamicin for Injection)
Myozyme (Alglucosidase alfa)
Nafcillin Injection (Nafcillin Sodium)
Nafcillin Sodium (Nafcillin Injection)
Naltrexone XR Inj (Vivitrol)
Naprosyn (naproxen)
NeoProfen (Ibuprofen Lysine Injection)
Nandrol Decanoate
Neostigmine Methylsulfate (Neostigmine Methylsulfate Injection)
NEO-GAA
NeoTect (Technetium Tc 99m Depreotide Injection)
Nephramine (Essential Amino Acid Injection)
Neulasta (pegfilgrastim)
Neupogen (Filgrastim)
Novolin
Novolog
NeoRecormon
Neutrexin (Trimetrexate Glucuronate Inj)
NPH (N)
Nexterone (Amiodarone HCl Injection)
Norditropin (Somatropin Injection)
Normal Saline (Sodium Chloride Injection)
Novantrone (Mitoxantrone for Injection Concentrate)
Novolin 70/30 Innolet (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection)
NovoLog (Insulin Aspart [rDNA origin] Inj)
Nplate (romiplostim)
Nutropin (Somatropin (rDNA origin) for Inj)
Nutropin AQ
Nutropin Depot (Somatropin (rDNA origin) for Inj)
Octreotide Acetate Injection (Sandostatin LAR)
Ocrelizumab
Ofatumumab Injection (Arzerra)
Olanzapine Extended Release Injectable Suspension (Zyprexa Relprevv)
Omnitarg
Omnitrope (Somatropin [rDNA origin] Injection)
Ondansetron Hydrochloride Injection (Zofran Injection)
OptiMARK (Gadoversetamide Injection)
Optiray Injection (Ioversol Injection)
Orencia
Osmitrol Injection in Aviva (Mannitol Injection in Aviva Plastic Vessel 250)
Osmitrol Injection in Viaflex (Mannitol Injection in Viaflex Plastic Vessel 250)
Osteoprotegrin
Ovidrel (Choriogonadotropin Alfa Injection)
Oxacillin (Oxacillin for Injection)
Oxaliplatin Injection (Eloxatin)
Oxytocin Injection (Pitocin)
Paliperidone Palmitate Extended-Release Injectable Suspension (Invega Sustenna)
Pamidronate Disodium Injection (Pamidronate Disodium Injection)
Panitumumab Injection for Intravenous Use (Vectibix)
Papaverine Hydrochloride Injection (Papaverine Injection)
Papaverine Injection (Papaverine Hydrochloride Injection)
Parathyroid Hormone
Paricalcitol Injection Fliptop Vial (Zemplar Injection)
PARP Inhibitor
Pediarix
PEGIntron
Peginterferon
Pegfilgrastim
Penicillin G Benzathine and Penicillin G Procaine
Pentetate Calcium Trisodium Inj (Ca-DTPA)
Pentetate Zinc Trisodium Injection (Zn-DTPA)
Pepcid Injection (Famotidine Injection)
Pergonal
Pertuzumab
Phentolamine Mesylate (Phentolamine Mesylate for Injection)
Physostigmine Salicylate (Physostigmine Salicylate (injection))

Physostigmine Salicylate (injection) (Physostigmine Salicylate)
Piperacillin and Tazobactam Injection (Zosyn)
Pitocin (Oxytocin Injection)
Plasma-Lyte 148 (Multiple Electrolytes Inj)
Plasma-Lyte 56 and Dextrose (Multiple Electrolytes and Dextrose Injection in Viaflex
Plastic Vessel 250)
PlasmaLyte
Plerixafor Injection (Mozobil)
Polidocanol Injection (Asclera)
Potassium Chloride
Pralatrexate Solution for Intravenous Injection (Folotyn)
Pramlintide Acetate Injection (Symlin)
Premarin Injection (Conjugated Estrogens for Injection)
Prep kit for Technetium Tc99 Sestamibi for Injection (Cardiolite)
Prevacid I.V. (Lansoprazole for Injection)
Primaxin I.V. (Imipenem and Cilastatin for Injection)
Prochymal
Procrit
Progesterone
ProHance (Gadoteridol Injection Solution)
Prolia (Denosumab Injection)
Promethazine HCl Injection (Promethazine Hydrochloride Injection)
Propranolol Hydrochloride Injection (Propranolol Hydrochloride Injection)
Quinidine Gluconate Injection (Quinidine Injection)
Quinidine Injection (Quinidine Gluconate Injection)
R-Gene 10 (Arginine Hydrochloride Injection)
Ranibizumab Injection (Lucentis)
Ranitidine Hydrochloride Injection (Zantac Injection)
Raptiva
Reclast (Zoledronic Acid Injection)
Recombivarix HB
Regadenoson Injection (Lexiscan)
Reglan Injection (Metoclopramide Injection)
Remicade
Renagel
Renvela (Sevelamer Carbonate)
Repronex (Menotropins for Injection)
Retrovir IV (Zidovudine Injection)
rhApo2L/TRAIL
Ringer's and 5% Dextrose Injection (Ringers in Dextrose)
Ringer's Injection (Ringers Injection)
Rituxan
Rituximab
Rocephin (ceftriaxone)
Rocuronium Bromide Injection (Zemuron)
Roferon-A (interferon alfa-2a)
Romazicon (flumazenil)
Romidepsin for Injection (Istodax)
Saizen (Somatropin Injection)
Sandostatin LAR (Octreotide Acetate Injection)
Sclerostin Ab
Sensipar (cinacalcet)
Sensorcaine (Bupivacaine HCl Injections)
Septocaine (Articane HCl and Epinephrine Injection)
Serostim LQ (Somatropin (rDNA origin) Injection)
Simponi Injection (Golimumab Injection)
Sodium Acetate (Sodium Acetate Injection)
Sodium Bicarbonate (Sodium Bicarbonate 5% Injection)
Sodium Lactate (Sodium Lactate Injection in AVIVA)
Sodium Phenylacetate and Sodium Benzoate Injection (Ammonul)
Somatropin (rDNA origin) for Inj (Nutropin)
Sporanox Injection (Itraconazole Injection)
Stelara Injection (Ustekinumab)
Stemgen
Sufenta (Sufentanil Citrate Injection)
Sufentanil Citrate Injection (Sufenta)
Sumavel
Sumatriptan Injection (Alsuma)
Symlin
Symlin Pen
Systemic Hedgehog Antagonist
Synvisc-One (Hylan G-F 20 Single Intra-articular Injection)
Tarceva
Taxotere (Docetaxel for Injection)
Technetium Tc 99m
Telavancin for Injection (Vibativ)
Temsirolimus Injection (Torisel)
Tenormin I.V. Injection (Atenolol Inj)
Teriparatide (rDNA origin) Injection (Forteo)
Testosterone Cypionate
Testosterone Enanthate
Testosterone Propionate
Tev-Tropin (Somatropin, rDNA Origin, for Injection)
tgAAC94
Thallous Chloride
Theophylline
Thiotepa (Thiotepa Injection)
Thymoglobulin (Anti-Thymocyte Globulin (Rabbit)
Thyrogen (Thyrotropin Alfa for Injection)
Ticarcillin Disodium and Clavulanate Potassium Galaxy (Timentin Injection)
Tigan Injection (Trimethobenzamide Hydrochloride Injectable)
Timentin Injection (Ticarcillin Disodium and Clavulanate Potassium Galaxy)
TNKase
Tobramycin Injection (Tobramycin Injection)
Tocilizumab Injection (Actemra)
Torisel (Temsirolimus Injection)
Totect (Dexrazoxane for Injection, Intravenous Infusion Only)
Trastuzumab-DM1
Travasol (Amino Acids (Injection))
Treanda (Bendamustine Hydrochloride Injection)
Trelstar (Triptorelin Pamoate for Injectable Suspension)
Triamcinolone Acetonide
Triamcinolone Diacetate
Triamcinolone Hexacetonide Injectable Suspension (Aristospan Injection 20 mg)
Triesence (Triamcinolone Acetonide Injectable Suspension)
Trimethobenzamide Hydrochloride Injectable (Tigan Injection)
Trimetrexate Glucuronate Inj (Neutrexin)
Triptorelin Pamoate for Injectable Suspension (Trelstar)
Twinject
Trivaris (Triamcinolone Acetonide Injectable Suspension)
Trisenox (Arsenic Trioxide Injection)
Twinrix
Typhoid Vi
Ultravist (Iopromide Injection)
Urofollitropin for Injection (Metrodin)
Urokinase Injection (Kinlytic)
Ustekinumab (Stelara Injection)
Ultralente (U)
Valium (diazepam)
Valproate Sodium Injection (Depacon)
Valtropin (Somatropin Injection)

Vancomycin Hydrochloride (Vancomycin Hydrochloride Injection)
Vancomycin Hydrochloride Injection (Vancomycin Hydrochloride)
Vaprisol (Conivaptan Hcl Injection)
VAQTA
Vasovist (Gadofosveset Trisodium Injection for Intravenous Use)
Vectibix (Panitumumab Injection for Intravenous Use)
Venofer (Iron Sucrose Injection)
Verteporfin Inj (Visudyne)
Vibativ (Telavancin for Injection)
Victoza (Liraglutide [rDNA] Injection)
Vimpat (lacosamide Tablet and Injection)
Vinblastine Sulfate (Vinblastine Sulfate Injection)
Vincasar PFS (Vincristine Sulfate Injection)
Victoza
Vincristine Sulfate (Vincristine Sulfate Injection)
Visudyne (Verteporfin Inj)
Vitamin B-12
Vivitrol (Naltrexone XR Inj)
Voluven (Hydroxyethyl Starch in Sodium Chloride Injection)
Xeloda
Xenical (orlistat)
Xeomin (Incobotulinumtoxin A for Injection)
Xolair
Zantac Injection (Ranitidine Hydrochloride Injection)
Zemplar Injection (Paricalcitol Injection Fliptop Vial)
Zemuron (Rocuronium Bromide Injection)
Zenapax (daclizumab)
Zevalin
Zidovudine Injection (Retrovir IV)
Zithromax Injection (Azithromycin)
Zn-DTPA (Pentetate Zinc Trisodium Injection)
Zofran Injection (Ondansetron Hydrochloride Injection)
Zingo
Zoledronic Acid for Inj (Zometa)
Zoledronic Acid Injection (Reclast)
Zometa (Zoledronic Acid for Inj)
Zosyn (Piperacillin and Tazobactam Injection)
Zyprexa Relprevv (Olanzapine Extended Release Injectable Suspension)
Liquid Drugs (Non-Injectable)
Abilify
AccuNeb (Albuterol Sulfate Inhalation Solution)
Actidose Aqua (Activated Charcoal Suspension)
Activated Charcoal Suspension (Actidose Aqua)
Advair
Agenerase Oral Solution (Amprenavir Oral Solution)
Akten (Lidocaine Hydrochloride Ophthalmic Gel)
Alamast (Pemirolast Potassium Ophthalmic Solution)
Albumin (Human) 5% Solution (Buminate 5%)
Albuterol Sulfate Inhalation Solution
Alinia
Alocril
Alphagan
Alrex
Alvesco
Amprenavir Oral Solution
Analpram-HC
Arformoterol Tartrate Inhalation Solution (Brovana)
Aristospan Injection 20 mg (Triamcinolone Hexacetonide Injectable Suspension)
Asacol
Asmanex
Astepro
Astepro (Azelastine Hydrochloride Nasal Spray)
Atrovent Nasal Spray (Ipratropium Bromide Nasal Spray)
Atrovent Nasal Spray 0.06
Augmentin ES-600
Azasite (Azithromycin Ophthalmic Solution)
Azelaic Acid (Finacea Gel)
Azelastine Hydrochloride Nasal Spray (Astepro)
Azelex (Azelaic Acid Cream)
Azopt (Brinzolamide Ophthalmic Suspension)
Bacteriostatic Saline
Balanced Salt
Bepotastine
Bactroban Nasal
Bactroban
Beclovent
Benzac W
Betimol
Betoptic S
Bepreve
Bimatoprost Ophthalmic Solution
Bleph 10 (Sulfacetamide Sodium Ophthalmic Solution 10%)
Brinzolamide Ophthalmic Suspension (Azopt)
Bromfenac Ophthalmic Solution (Xibrom)
Bromhist
Brovana (Arformoterol Tartrate Inhalation Solution)
Budesonide Inhalation Suspension (Pulmicort Respules)
Cambia (Diclofenac Potassium for Oral Solution)
Capex
Carac
Carboxine-PSE
Carnitor
Cayston (Aztreonam for Inhalation Solution)
Cellcept
Centany
Cerumenex
Ciloxan Ophthalmic Solution (Ciprofloxacin HCL Ophthalmic Solution)
Ciprodex
Ciprofloxacin HCL Ophthalmic Solution (Ciloxan Ophthalmic Solution)
Clemastine Fumarate Syrup (Clemastine Fumarate Syrup)
CoLyte (PEG Electrolytes Solution)
Combiven
Comtan
Condylox
Cordran
Cortisporin Ophthalmic Suspension
Cortisporin Otic Suspension
Cromolyn Sodium Inhalation Solution (Intal Nebulizer Solution)
Cromolyn Sodium Ophthalmic Solution (Opticrom)
Crystalline Amino Acid Solution with Electrolytes (Aminosyn Electrolytes)
Cutivate
Cuvposa (Glycopyrrolate Oral Solution)
Cyanocobalamin (CaloMist Nasal Spray)
Cyclosporine Oral Solution (Gengraf Oral Solution)
Cyclogyl
Cysview (Hexaminolevulinate Hydrochloride Intravesical Solution)
DermOtic Oil (Fluocinolone Acetonide Oil Ear Drops)
Desmopressin Acetate Nasal Spray
DDAVP
Derma-Smoothe/FS
Dexamethasone Intensol
Dianeal Low Calcium

Dianeal PD
Diclofenac Potassium for Oral Solution (Cambia)
Didanosine Pediatric Powder for Oral Solution (Videx)
Differin
Dilantin 125 (Phenytoin Oral Suspension)
Ditropan
Dorzolamide Hydrochloride Ophthalmic Solution (Trusopt)
Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution (Cosopt)
Dovonex Scalp (Calcipotriene Solution)
Doxycycline Calcium Oral Suspension (Vibramycin Oral)
Efudex
Elaprase (Idursulfase Solution)
Elestat (Epinastine HCl Ophthalmic Solution)
Elocon
Epinastine HCl Ophthalmic Solution (Elestat)
Epivir HBV
Epogen (Epoetin alfa)
Erythromycin Topical Solution 1.5% (Staticin)
Ethiodol (Ethiodized Oil)
Ethosuximide Oral Solution (Zarontin Oral Solution)
Eurax
Extraneal (Icodextrin Peritoneal Dialysis Solution)
Felbatol
Feridex I.V. (Ferumoxides Injectable Solution)
Flovent
Floxin Otic (Ofloxacin Otic Solution)
Flo-Pred (Prednisolone Acetate Oral Suspension)
Fluoroplex
Flunisolide Nasal Solution (Flunisolide Nasal Spray 0.025%)
Fluorometholone Ophthalmic Suspension (FML)
Flurbiprofen Sodium Ophthalmic Solution (Ocufen)
FML
Foradil
Formoterol Fumarate Inhalation Solution (Perforomist)
Fosamax
Furadantin (Nitrofurantoin Oral Suspension)
Furoxone
Gammagard Liquid (Immune Globulin Intravenous (Human) 10%)
Gantrisin (Acetyl Sulfisoxazole Pediatric Suspension)
Gatifloxacin Ophthalmic Solution (Zymar)
Gengraf Oral Solution (Cyclosporine Oral Solution)
Glycopyrrolate Oral Solution (Cuvposa)
Halcinonide Topical Solution (Halog Solution)
Halog Solution (Halcinonide Topical Solution)
HEP-LOCK U/P (Preservative-Free Heparin Lock Flush Solution)
Heparin Lock Flush Solution (Hepflush 10
Hexaminolevulinate Hydrochloride Intravesical Solution (Cysview)
Hydrocodone Bitartrate and Acetaminophen Oral Solution (Lortab Elixir)
Hydroquinone 3% Topical Solution (Melquin-3 Topical Solution)
IAP Antagonist
Isopto
Ipratropium Bromide Nasal Spray (Atrovent Nasal Spray)
Itraconazole Oral Solution (Sporanox Oral Solution)
Ketorolac Tromethamine Ophthalmic Solution (Acular LS)
Kaletra
Lanoxin
Lexiva
Leuprolide Acetate for Depot Suspension (Lupron Depot 11.25 mg)
Levobetaxolol Hydrochloride Ophthalmic Suspension (Betaxon)
Levocarnitine Tablets, Oral Solution, Sugar-Free (Carnitor)
Levofloxacin Ophthalmic Solution 0.5% (Quixin)
Lidocaine HCl Sterile Solution (Xylocaine MPF Sterile Solution)
Lok Pak (Heparin Lock Flush Solution)
Lorazepam Intensol
Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Oral Solution)
Lotemax (Loteprednol Etabonate Ophthalmic Suspension)
Loteprednol Etabonate Ophthalmic Suspension (Alrex)
Low Calcium Peritoneal Dialysis Solutions (Dianeal Low Calcium)
Lumigan (Bimatoprost Ophthalmic Solution 0.03% for Glaucoma)
Lupron Depot 11.25 mg (Leuprolide Acetate for Depot Suspension)
Megestrol Acetate Oral Suspension (Megestrol Acetate Oral Suspension)
MEK Inhibitor
Mepron
Mesnex
Mestinon
Mesalamine Rectal Suspension Enema (Rowasa)
Melquin-3 Topical Solution (Hydroquinone 3% Topical Solution)
MetMab
Methyldopate Hcl (Methyldopate Hydrochloride Injection, Solution)
Methylin Oral Solution (Methylphenidate HCl Oral Solution 5 mg/5 mL and 10 mg/5 mL)
Methylprednisolone Acetate Injectable Suspension (Depo Medrol)
Methylphenidate HCl Oral Solution 5 mg/5 mL and 10 mg/5 mL (Methylin Oral Solution)
Methylprednisolone sodium succinate (Solu Medrol)
Metipranolol Ophthalmic Solution (Optipranolol)
Migranal
Miochol-E (Acetylcholine Chloride Intraocular Solution)
Micro-K for Liquid Suspension (Potassium Chloride Extended Release Formulation for Liquid Suspension)
Minocin (Minocycline Hydrochloride Oral Suspension)
Nasacort
Neomycin and Polymyxin B Sulfates and Hydrocortisone
Nepafenac Ophthalmic Suspension (Nevanac)
Nevanac (Nepafenac Ophthalmic Suspension)
Nitrofurantoin Oral Suspension (Furadantin)
Noxafil (Posaconazole Oral Suspension)
Nystatin (oral) (Nystatin Oral Suspension)
Nystatin Oral Suspension (Nystatin (oral))
Ocufen (Flurbiprofen Sodium Ophthalmic Solution)
Ofloxacin Ophthalmic Solution (Ofloxacin Ophthalmic Solution)
Ofloxacin Otic Solution (Floxin Otic)
Olopatadine Hydrochloride Ophthalmic Solution (Pataday)
Opticrom (Cromolyn Sodium Ophthalmic Solution)
Optipranolol (Metipranolol Ophthalmic Solution)
Patanol
Pediapred
PerioGard
Phenytoin Oral Suspension (Dilantin 125)
Phisohex
Posaconazole Oral Suspension (Noxafil)
Potassium Chloride Extended Release Formulation for Liquid Suspension (Micro-K for Liquid Suspension)
Pataday (Olopatadine Hydrochloride Ophthalmic Solution)

Patanase Nasal Spray (Olopatadine Hydrochloride Nasal Spray)
PEG Electrolytes Solution (CoLyte)
Pemirolast Potassium Ophthalmic Solution (Alamast)
Penlac (Ciclopirox Topical Solution)
PENNSAID (Diclofenac Sodium Topical Solution)
Perforomist (Formoterol Fumarate Inhalation Solution)
Peritoneal Dialysis Solution
Phenylephrine Hydrochloride Ophthalmic Solution (Neo-Synephrine)
Phospholine Iodide (Echothiophate Iodide for Ophthalmic Solution)
Podofilox (Podofilox Topical Solution)
Pred Forte (Prednisolone Acetate Ophthalmic Suspension)
Pralatrexate Solution for Intravenous Injection (Folotyn)
Pred Mild
Prednisone Intensol
Prednisolone Acetate Ophthalmic Suspension (Pred Forte)
Prevacid
PrismaSol Solution (Sterile Hemofiltration Hemodiafiltration Solution)
ProAir
Proglycem
ProHance (Gadoteridol Injection Solution)
Proparacaine Hydrochloride Ophthalmic Solution (Alcaine)
Propine
Pulmicort
Pulmozyme
Quixin (Levofloxacin Ophthalmic Solution 0.5%)
QVAR
Rapamune
Rebetol
Relacon-HC
Rotarix (Rotavirus Vaccine, Live, Oral Suspension)
Rotavirus Vaccine, Live, Oral Suspension (Rotarix)
Rowasa (Mesalamine Rectal Suspension Enema)
Sabril (Vigabatrin Oral Solution)
Sacrosidase Oral Solution (Sucraid)
Sandimmune
Sepra
Serevent Diskus
Solu Cortef (Hydrocortisone Sodium Succinate)
Solu Medrol (Methylprednisolone sodium succinate)
Spiriva
Sporanox Oral Solution (Itraconazole Oral Solution)
Staticin (Erythromycin Topical Solution 1.5%)
Stalevo
Starlix
Sterile Hemofiltration Hemodiafiltration Solution (PrismaSol Solution)
Stimate
Sucralfate (Carafate Suspension)
Sulfacetamide Sodium Ophthalmic Solution 10% (Bleph 10
Synarel Nasal Solution (Nafarelin Acetate Nasal Solution for Endometriosis)
Taclonex Scalp (Calcipotriene and Betamethasone Dipropionate Topical Suspension)
Tamiflu
Tobi
TobraDex
Tobradex ST (Tobramycin/Dexamethasone Ophthalmic Suspension 0.3%/0.05%)
Tobramycin/Dexamethasone Ophthalmic Suspension 0.3%/0.05% (Tobradex ST)
Timolol
Timoptic
Travatan Z
Treprostinil Inhalation Solution (Tyvaso)
Trusopt (Dorzolamide Hydrochloride Ophthalmic Solution)
Tyvaso (Treprostinil Inhalation Solution)
Ventolin
Vfend
Vibramycin Oral (Doxycycline Calcium Oral Suspension)
Videx (Didanosine Pediatric Powder for Oral Solution)
Vigabatrin Oral Solution (Sabril)
Viokase
Viracept
Viramune
Vitamin K1 (Fluid Colloidal Solution of Vitamin K1)
Voltaren Ophthalmic (Diclofenac Sodium Ophthalmic Solution)
Zarontin Oral Solution (Ethosuximide Oral Solution)
Ziagen
Zyvox
Zymar (Gatifloxacin Ophthalmic Solution)
Zymaxid (Gatifloxacin Ophthalmic Solution)

Drug Classes

5-alpha-reductase inhibitors
5-aminosalicylates
5HT3 receptor antagonists
adamantane antivirals
adrenal cortical steroids
adrenal corticosteroid inhibitors
adrenergic bronchodilators
agents for hypertensive emergencies
agents for pulmonary hypertension
aldosterone receptor antagonists
alkylating agents
alpha-adrenoreceptor antagonists
alpha-glucosidase inhibitors
alternative medicines
amebicides
aminoglycosides
aminopenicillins
aminosalicylates
amylin analogs
Analgesic Combinations
Analgesics
androgens and anabolic steroids
angiotensin converting enzyme inhibitors
angiotensin II inhibitors
anorectal preparations
anorexiants
antacids
anthelmintics
anti-angiogenic ophthalmic agents
anti-CTLA-4 monoclonal antibodies
anti-infectives
antiadrenergic agents, centrally acting
antiadrenergic agents, peripherally acting
antiandrogens
antianginal agents
antiarrhythmic agents
antiasthmatic combinations
antibiotics/antineoplastics
anticholinergic antiemetics
anticholinergic antiparkinson agents
anticholinergic bronchodilators
anticholinergic chronotropic agents
anticholinergics/antispasmodics
anticoagulants
anticonvulsants
antidepressants
antidiabetic agents

antidiabetic combinations
antidiarrheals
antidiuretic hormones
antidotes
antiemetic/antivertigo agents
antifungals
antigonadotropic agents
antigout agents
antihistamines
antihyperlipidemic agents
antihyperlipidemic combinations
antihypertensive combinations
antihyperuricemic agents
antimalarial agents
antimalarial combinations
antimalarial quinolines
antimetabolites
antimigraine agents
antineoplastic detoxifying agents
antineoplastic interferons
antineoplastic monoclonal antibodies
antineoplastics
antiparkinson agents
antiplatelet agents
antipseudomonal penicillins
antipsoriatics
antipsychotics
antirheumatics
antiseptic and germicides
antithyroid agents
antitoxins and antivenins
antituberculosis agents
antituberculosis combinations
antitussives
antiviral agents
antiviral combinations
antiviral interferons
anxiolytics, sedatives, and hypnotics
aromatase inhibitors
atypical antipsychotics
azole antifungals
bacterial vaccines
barbiturate anticonvulsants
barbiturates
BCR-ABL tyrosine kinase inhibitors
benzodiazepine anticonvulsants
benzodiazepines
beta-adrenergic blocking agents
beta-lactamase inhibitors
bile acid sequestrants
biologicals
bisphosphonates
bone resorption inhibitors
bronchodilator combinations
bronchodilators
calcitonin
calcium channel blocking agents
carbamate anticonvulsants
carbapenems
carbonic anhydrase inhibitor anticonvulsants
carbonic anhydrase inhibitors
cardiac stressing agents
cardioselective beta blockers
cardiovascular agents
catecholamines
CD20 monoclonal antibodies
CD33 monoclonal antibodies
CD52 monoclonal antibodies
central nervous system agents
cephalosporins
cerumenolytics
chelating agents
chemokine receptor antagonist
chloride channel activators
cholesterol absorption inhibitors
cholinergic agonists
cholinergic muscle stimulants
cholinesterase inhibitors
CNS stimulants
coagulation modifiers
colony stimulating factors
contraceptives
corticotropin
coumarins and indandiones
cox-2 inhibitors
decongestants
dermatological agents
diagnostic radiopharmaceuticals
dibenzazepine anticonvulsants
digestive enzymes
dipeptidyl peptidase 4 inhibitors
diuretics
dopaminergic antiparkinsonism agents
drugs used in alcohol dependence
echinocandins
EGFR inhibitors
estrogen receptor antagonists
estrogens
expectorants
factor Xa inhibitors
fatty acid derivative anticonvulsants
fibric acid derivatives
first generation cephalosporins
fourth generation cephalosporins
functional bowel disorder agents
gallstone solubilizing agents
gamma-aminobutyric acid analogs
gamma-aminobutyric acid reuptake inhibitors
gamma-aminobutyric acid transaminase inhibitors
gastrointestinal agents
general anesthetics
genitourinary tract agents
GI stimulants
glucocorticoids
glucose elevating agents
glycopeptide antibiotics
glycoprotein platelet inhibitors
glycylcyclines
gonadotropin releasing hormones
gonadotropin-releasing hormone antagonists
gonadotropins
group I antiarrhythmics
group II antiarrhythmics
group III antiarrhythmics
group IV antiarrhythmics
group V antiarrhythmics
growth hormone receptor blockers
growth hormones
H. pylori eradication agents
H2 antagonists
hematopoietic stem cell mobilizer
heparin antagonists
heparins
HER2 inhibitors

herbal products
histone deacetylase inhibitors
hormone replacement therapy
hormones
hormones/antineoplastics
hydantoin anticonvulsants
illicit (street) drugs
immune globulins
immunologic agents
immunosuppressive agents
impotence agents
in vivo diagnostic biologicals
incretin mimetics
inhaled anti-infectives
inhaled corticosteroids
inotropic agents
insulin
insulin-like growth factor
integrase strand transfer inhibitor
interferons
intravenous nutritional products
iodinated contrast media
ionic iodinated contrast media
iron products
ketolides
laxatives
leprostatics
leukotriene modifiers
lincomycin derivatives
lipoglycopeptides
local injectable anesthetics
loop diuretics
lung surfactants
lymphatic staining agents
lysosomal enzymes
macrolide derivatives
macrolides
magnetic resonance imaging contrast media
mast cell stabilizers
medical gas
meglitinides
metabolic agents
methylxanthines
mineralocorticoids
minerals and electrolytes
miscellaneous agents
miscellaneous analgesics
miscellaneous antibiotics
miscellaneous anticonvulsants
miscellaneous antidepressants
miscellaneous antidiabetic agents
miscellaneous antiemetics
miscellaneous antifungals
miscellaneous antihyperlipidemic agents
miscellaneous antimalarials
miscellaneous antineoplastics
miscellaneous antiparkinson agents
miscellaneous antipsychotic agents
miscellaneous antituberculosis agents
miscellaneous antivirals
miscellaneous anxiolytics, sedatives and hypnotics
miscellaneous biologicals
miscellaneous bone resorption inhibitors
miscellaneous cardiovascular agents
miscellaneous central nervous system agents
miscellaneous coagulation modifiers
miscellaneous diuretics
miscellaneous genitourinary tract agents
miscellaneous GI agents
miscellaneous hormones
miscellaneous metabolic agents
miscellaneous ophthalmic agents
miscellaneous otic agents
miscellaneous respiratory agents
miscellaneous sex hormones
miscellaneous topical agents
miscellaneous uncategorized agents
miscellaneous vaginal agents
mitotic inhibitors
monoamine oxidase inhibitors
monoclonal antibodies
mouth and throat products
mTOR inhibitors
mTOR kinase inhibitors
mucolytics
multikinase inhibitors
muscle relaxants
mydriatics
narcotic analgesic combinations
narcotic analgesics
nasal anti-infectives
nasal antihistamines and decongestants
nasal lubricants and irrigations
nasal preparations
nasal steroids
natural penicillins
neuraminidase inhibitors
neuromuscular blocking agents
next generation cephalosporins
nicotinic acid derivatives
nitrates
NNRTIs
non-cardioselective beta blockers
non-iodinated contrast media
non-ionic iodinated contrast media
non-sulfonylureas
nonsteroidal anti-inflammatory agents
norepinephrine reuptake inhibitors
norepinephrine-dopamine reuptake inhibitors
nucleoside reverse transcriptase inhibitors (NRTIs)
nutraceutical products
nutritional products
ophthalmic anesthetics
ophthalmic anti-infectives
ophthalmic anti-inflammatory agents
ophthalmic antihistamines and decongestants
ophthalmic diagnostic agents
ophthalmic glaucoma agents
ophthalmic lubricants and irrigations
ophthalmic preparations
ophthalmic steroids
ophthalmic steroids with anti-infectives
ophthalmic surgical agents
oral nutritional supplements
otic anesthetics
otic anti-infectives
otic preparations
otic steroids
otic steroids with anti-infectives
oxazolidinedione anticonvulsants
parathyroid hormone and analogs
penicillinase resistant penicillins
penicillins
peripheral opioid receptor antagonists

peripheral vasodilators
peripherally acting antiobesity agents
phenothiazine antiemetics
phenothiazine antipsychotics
phenylpiperazine antidepressants
plasma expanders
platelet aggregation inhibitors
platelet-stimulating agents
polyenes
potassium-sparing diuretics
probiotics
progesterone receptor modulators
progestins
prolactin inhibitors
prostaglandin D2 antagonists
protease inhibitors
proton pump inhibitors
psoralens
psychotherapeutic agents
psychotherapeutic combinations
purine nucleosides
pyrrolidine anticonvulsants
quinolones
radiocontrast agents
radiologic adjuncts
radiologic agents
radiologic conjugating agents
radiopharmaceuticals
RANK ligand inhibitors
recombinant human erythropoietins
renin inhibitors
respiratory agents
respiratory inhalant products
rifamycin derivatives
salicylates
sclerosing agents
second generation cephalosporins
selective estrogen receptor modulators
selective serotonin reuptake inhibitors
serotonin-norepinephrine reuptake inhibitors
serotoninergic neuroenteric modulators
sex hormone combinations
sex hormones
skeletal muscle relaxant combinations
skeletal muscle relaxants
smoking cessation agents
somatostatin and somatostatin analogs
spermicides
statins
sterile irrigating solutions
streptomyces derivatives
succinimide anticonvulsants
sulfonamides
sulfonylureas
synthetic ovulation stimulants
tetracyclic antidepressants
tetracyclines
therapeutic radiopharmaceuticals
thiazide diuretics
thiazolidinediones
thioxanthenes
third generation cephalosporins
thrombin inhibitors
thrombolytics
thyroid drugs
tocolytic agents
topical acne agents
topical agents
topical anesthetics
topical anti-infectives
topical antibiotics
topical antifungals
topical antihistamines
topical antipsoriatics
topical antivirals
topical astringents
topical debriding agents
topical depigmenting agents
topical emollients
topical keratolytics
topical steroids
topical steroids with anti-infectives
toxoids
triazine anticonvulsants
tricyclic antidepressants
trifunctional monoclonal antibodies
tumor necrosis factor (TNF) inhibitors
tyrosine kinase inhibitors
ultrasound contrast media
upper respiratory combinations
urea anticonvulsants
urinary anti-infectives
urinary antispasmodics
urinary pH modifiers
uterotonic agents
vaccine
vaccine combinations
vaginal anti-infectives
vaginal preparations
vasodilators
vasopressin antagonists
vasopressors
VEGF/VEGFR inhibitors
viral vaccines
viscosupplementation agents
vitamin and mineral combinations
vitamins
Diagnostic Tests
17-Hydroxyprogesterone
ACE (Angiotensin I converting enzyme)
Acetaminophen
Acid phosphatase
ACTH
Activated clotting time
Activated protein C resistance
Adrenocorticotropic hormone (ACTH)
Alanine aminotransferase (ALT)
Albumin
Aldolase
Aldosterone
Alkaline phosphatase
Alkaline phosphatase (ALP)
Alpha1-antitrypsin
Alpha-fetoprotein
Alpha-fetoprotien
Ammonia levels
Amylase
ANA (antinuclear antbodies)
ANA (antinuclear antibodies)
Angiotensin-converting enzyme (ACE)
Anion gap
Anticardiolipin antibody
Anticardiolipin antivbodies (ACA)
Anti-centromere antibody

Antidiuretic hormone
Anti-DNA
Anti-Dnase-B
Anti-Gliadin antibody
Anti-glomerular basement membrane antibody
Anti-HBc (Hepatitis B core antibodies
Anti-HBs (Hepatitis B surface antibody
Antiphospholipid antibody
Anti-RNA polymerase
Anti-Smith (Sm) antibodies
Anti-Smooth Muscle antibody
Antistreptolysin O (ASO)
Antithrombin III
Anti-Xa activity
Anti-Xa assay
Apolipoproteins
Arsenic
Aspartate aminotransferase (AST)
B12
Basophil
Beta-2-Microglobulin
Beta-hydroxybutyrate
B-HCG
Bilirubin
Bilirubin, direct
Bilirubin, indirect
Bilirubin, total
Bleeding time
Blood gases (arterial)
Blood urea nitrogen (BUN)
BUN
BUN (blood urea nitrogen)
CA 125
CA 15-3
CA 19-9
Calcitonin
Calcium
Calcium (ionized)
Carbon monoxide (CO)
Carcinoembryonic antigen (CEA)
CBC
CEA
CEA (carcinoembryonic antigen)
Ceruloplasmin
CH50Chloride
Cholesterol
Cholesterol, HDL
Clot lysis time
Clot retraction time
CMP
CO2
Cold agglutinins
Complement C3
Copper
Corticotrophin releasing hormone (CRH) stimulation test
Cortisol
Cortrosyn stimulation test
C-peptide
CPK (Total)
CPK-MB
C-reactive protein
Creatinine
Creatinine kinase (CK)
Cryoglobulins
DAT (Direct antiglobulin test)
D-Dimer
Dexamethasone suppression test
DHEA-S
Dilute Russell viper venom
Elliptocytes
Eosinophil
Erythrocyte sedimentation rate (ESR)
Estradiol
Estriol
Ethanol
Ethylene glycol
Euglobulin lysis
Factor V Leiden
Factor VIII inhibitor
Factor VIII level
Ferritin
Fibrin split products
Fibrinogen
Folate
Folate (serum
Fractional excretion of sodium (FENA)
FSH (follicle stimulating factor)
FTA-ABS
Gamma glutamyl transferase (GGT)
Gastrin
GGTP (Gamma glutamyl transferase)
Glucose
Growth hormone
Haptoglobin
HBeAg (Hepatitis Be antigen)
HBs-Ag (Hepatitis B surface antigen)
Helicobacter pylori
Hematocrit
Hematocrit (HCT)
Hemoglobin
Hemoglobin Al C
Hemoglobin electrophoresis
Hepatitis A antibodies
Hepatitis C antibodies
IAT (Indirect antiglobulin test)
Immunofixation (IFE)
Iron
Lactate dehydrogenase (LDH)
Lactic acid (lactate)
LDH
LH (Leutinizing hormone
Lipase
Lupus anticoagulant
Lymphocyte
Magnesium
MCH (mean corpuscular hemoglobin
MCHC (mean corpuscular hemoglobin concentration)
MCV (mean corpuscular volume)
Methylmalonate
Monocyte
MPV (mean platelet volume)
Myoglobin
Neutrophil
Parathyroid hormone (PTH)
Phosphorus
Platelets (plt)
Potassium
Prealbumin
Prolactin
Prostate specific antigen (PSA)
Protein C
Protein S
PSA (prostate specific antigen)
PT (Prothrombin time)

PTT (Partial thromboplastin time)
RDW (red cell distribution width)
Renin
Rennin
Reticulocyte count
reticulocytes
Rheumatoid factor (RF)
Sed Rate
Serum glutamic-pyruvic transaminase (SGPT
Serum protein electrophoresis (SPEP)
Sodium
T3-resin uptake (T3RU)
T4, Free
Thrombin time
Thyroid stimulating hormone (TSH)
Thyroxine (T4
Total iron binding capacity (TIBC)
Total protein
Transferrin
Transferrin saturation
Triglyceride (TG)
Troponin
Uric acid
Vitamin B12
White blood cells (WBC)
Widal test

As several examples, the fluid composition **218** can be an inhalation anesthetic, a drug, or a diagnostic test material. Any of these fluid compositions **218** can be an injectable material, a volatile material capable of being inhaled, or otherwise capable of being introduced into a subject.

In the embodiment of FIG. **7** in particular, the pharmaceutical package **210** is a syringe. The syringe can comprise a syringe barrel **250** and a plunger **258**. The wall **214** can define at least a portion of the syringe barrel **250**. The plunger **258** can be a relatively sliding part of the syringe, with respect to the syringe barrel **250**. The term "syringe," however, is broadly defined to include cartridges, injection "pens," and other types of barrels or reservoirs adapted to be assembled with one or more other components to provide a functional syringe. "Syringe" is also broadly defined to include related articles such as auto-injectors, which provide a mechanism for dispensing the contents.

Another aspect of the invention illustrated by FIGS. **24-26** is an article such as any of the pharmaceutical packages or other vessels **210** including a wall **214**, a fluid composition **218**, a barrier coating or layer **288**, and a protective coating **286**.

The wall **214** has an inner or interior surface **254**.

The fluid composition **218** is contained in the lumen **212** and has a pH between 5 and 9.

The barrier coating or layer **288** is made at least in part of SiO_x, wherein x is from 1.5 to 2.9, from 2 to 1000 nm thick. The barrier coating or layer **288** of SiO_x has an interior surface **220** facing the lumen **212** and an outer surface **222** facing the wall inner or interior surface **254**. The barrier coating or layer **288** is effective to reduce the ingress of atmospheric gas into the lumen **212**, compared to an uncoated container otherwise the same as the pharmaceutical package or other vessel **210**.

The protective coating **286** is made at least in part of a saccharide. The protective coating **286** has an interior surface **224** facing the lumen **212** and an outer surface **226** facing the interior surface **254** of the barrier coating or layer **288**. Other specific examples of precursors within this broad definition are provided elsewhere in this specification.

The rate of erosion, dissolution, or leaching (different names for related concepts) of the protective coating **286**, if directly contacted by the fluid composition **218**, is less than the rate of erosion of the barrier coating or layer **288**, if directly contacted by the fluid composition **218**.

The protective coating **286** is effective to isolate the fluid composition **218** from the barrier coating or layer **288**, at least for sufficient time to allow the barrier coating to act as a barrier during the shelf life of the pharmaceutical package or other vessel **210**.

Still another aspect of the invention, again illustrated by FIGS. **7** to **9**, is a pharmaceutical package or other vessel **210** including a thermoplastic wall **214** having an inner or interior surface **220** enclosing a lumen **212**. A fluid composition **218** contained in the lumen **212** has a pH greater than 5.

A barrier coating or layer **286** of SiO_x, in which x is between 1.5 and 2.9, is applied by plasma enhanced chemical vapor deposition (PECVD) directly or indirectly to the thermoplastic wall **214** so that in the filled pharmaceutical package or other vessel **210** the barrier coating or layer **286** is located between the inner or interior surface **220** of the thermoplastic wall **214** and the fluid composition **218**. The barrier coating or layer **286** of SiO_x is supported by the thermoplastic wall **214**. The barrier coating or layer **286** has the characteristic of being subject to being measurably diminished in barrier improvement factor in less than six months as a result of attack by the fluid composition **218**. The barrier coating or layer **286** as described elsewhere in this specification, or in U.S. Pat. No. 7,985,188, can be used in any embodiment.

The barrier improvement factor (BIF) of the barrier layer can be determined by providing two groups of identical containers, adding a barrier layer to one group of containers, testing a barrier property (such as the rate of outgassing in micrograms per minute or another suitable measure) on containers having a barrier, doing the same test on containers lacking a barrier, and taking a ratio of the properties of the materials with versus without a barrier. For example, if the rate of outgassing through the barrier is one-third the rate of outgassing without a barrier, the barrier has a BIF of 3.

A protective coating **286** of a saccharide is applied by directly or indirectly to the barrier coating or layer **288** so it is located between the barrier coating or layer **288** and the fluid composition **218** in the finished article. The protective coating **286** is supported by the thermoplastic wall **214**. The protective coating **286** is effective to keep the barrier coating or layer **288** at least substantially undissolved as a result of attack by the fluid composition **218** for a period of at least six months.

Any embodiment of FIGS. **24-26** can further optionally include a lubricity layer **287**. The lubricity layer **287** can be applied between the protective coating and the lumen. Lubricity layers **287** as described in U.S. Pat. No. 7,985,188 can be used in any embodiment.

Any embodiment of FIGS. **24-26** can further optionally include a further coating applied adjacent to the inner surface of the protective coating, the further coating having an outer surface facing the interior surface of the thermoplastic wall and an inner surface facing the lumen.

Optionally, any embodiment of FIGS. **24-26** can further include a fluid composition **218** in contact with the protective coating

The protective and lubricity layers **286** and **287** of any embodiment of FIGS. **24-26** can be either separate layers with a sharp transition or a single, graduated layer that

transitions between the protective coating **286** and the lubricity layer **287**, without a sharp interface between them.

Optionally, in any embodiment of FIGS. **24-26** the silicon dissolution rate by a 50 mM potassium phosphate buffer diluted in water for injection, adjusted to pH 8 with concentrated nitric acid, and containing 0.2 wt. % polysorbate-80 surfactant, (measured in the absence of the medicament, to avoid changing the dissolution reagent), at 40° C., is less than 170 ppb/day. (Polysorbate-80 is a common ingredient of pharmaceutical preparations, available for example as Tween®-80 from Uniqema Americas LLC, Wilmington, Del.) As will be seen from the working examples, the silicon dissolution rate is measured by determining the total silicon leached from the vessel into its contents, and does not distinguish between the silicon derived from the protective coating **286**, the lubricity layer **287**, the barrier coating or layer **288**, or other materials present.

Optionally, in any embodiment of FIGS. **24-26** the silicon dissolution rate is less than 160 ppb/day, or less than 140 ppb/day, or less than 120 ppb/day, or less than 100 ppb/day, or less than 90 ppb/day, or less than 80 ppb/day. Optionally, in any embodiment of FIGS. **24-26** the silicon dissolution rate is more than 10 ppb/day, or more than 20 ppb/day, or more than 30 ppb/day, or more than 40 ppb/day, or more than 50 ppb/day, or more than 60 ppb/day. Any minimum rate stated here can be combined with any maximum rate stated here, as an alternative embodiment of the invention of FIGS. **7** TO **9**.

Optionally, in any embodiment of FIGS. **24-26** the total silicon content of the protective coating and barrier coating, upon dissolution into a test composition with a pH of 8 from the vessel, is less than 66 ppm, or less than 60 ppm, or less than 50 ppm, or less than 40 ppm, or less than 30 ppm, or less than 20 ppm.

Optionally, in any embodiment of FIGS. **24-26** the calculated shelf life of the package (total Si/Si dissolution rate) is more than six months, or more than 1 year, or more than 18 months, or more than 2 years, or more than 2½ years, or more than 3 years, or more than 4 years, or more than 5 years, or more than 10 years, or more than 20 years. Optionally, in any embodiment of FIGS. **24-26** the calculated shelf life of the package (total Si/Si dissolution rate) is less than 60 years.

Any minimum time stated here can be combined with any maximum time stated here, as an alternative embodiment of the invention of FIGS. **7** TO **9**.

Optionally, in any embodiment of FIGS. **24-26**, the thermoplastic wall is a syringe barrel. A plunger is positioned for sliding in the barrel and a lubricity coating or layer is present on at least a portion of the plunger.

Optionally, in any embodiment of FIGS. **24-26**, the lubricity coating or layer is configured to provide a lower piston sliding force or breakout force than the uncoated substrate.

Optionally, in any embodiment of FIGS. **24-26**, the lubricity layer has one of the atomic ratios previously defined for the lubricity and/or protective coating, measured by X-ray photoelectron spectroscopy (XPS). The lubricity layer has a thickness by transmission electron microscopy (TEM) between 10 and 500 nm; the lubricity layer deposited by plasma enhanced chemical vapor deposition (PECVD) under conditions effective to form a coating from a precursor selected from a linear siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, a linear silazane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, a silatrane, a silquasilatrane, a silproatrane, an azasilatrane, an azasilquasiatrane, an azasilproatrane, or a combination of any two or more of these precursors.

Even another aspect of the invention, exemplified in FIGS. **7** TO **9**, is a composite material including a substrate such as a wall **214**, a barrier coating or layer **288** disposed on the substrate or wall **214**, and a passivation layer or protective coating **286** on the barrier layer or coating **288**. Several examples of articles made from such a composite material are a syringe barrel, a vial, and a medical device of any kind. The saccharide passivation layer or protective coating **286** is deposited as explained below.

PECVD Apparatus and Methods for Protective Coating

Suitable methods and apparatus for applying a barrier or lubricity coating or layer such as **90** to a substrate such as the vessel **80** (FIG. **1**) or a vial are described, for example, in U.S. Pat. No. 7,985,188 or the EP applications cited in paragraph [002], under conditions effective to form a coating or layer.

Another embodiment is a vessel such as the vessel **80** (FIG. **1**) including a lumen defined by a surface defining a substrate. A protective coating or layer is present on at least a portion of the substrate, typically deposited over an SiO_x barrier layer to protect the barrier layer from dissolution. The protective coating or layer is made by the previously defined process.

Still another embodiment is a chemical vapor deposition apparatus such as the apparatus **28** illustrated in FIG. **5** (or any other illustrated coating apparatus, such as the apparatus illustrated in FIGS. **1-4**).

Referring now to FIG. **5**, suitable chemical vapor deposition apparatus is shown.

Referring to FIG. **7**, yet another embodiment is a syringe such as **252** comprising a plunger **258**, a barrel **250**, and a protective coating or layer on the inner or interior surface **264**. The barrel **250** is a vessel and has an inner or interior surface **264** defining the vessel lumen **274** and receiving the plunger **258** for sliding. The vessel inner or interior surface **264** is a substrate. A protective coating or layer can be applied on the substrate **264**, the plunger **258**, or both, by chemical vapor deposition. In addition to this protective coating or layer, the syringe may contain one or more other coatings or layers, for example an SiO_x barrier coating or layer. Said additional coating(s) or layer(s) may be located under the lubricity and/or barrier coating or layer, i.e. nearer to the barrel of the syringe.

For any embodiment of a syringe such as **252**, in particular a syringe that is stored or intended to be stored for an extended time while prefilled, the plunger **258** optionally is provided with a lubricity layer, at least on its surface in contact with the barrel interior surface **264**, and the barrel interior surface **264** is provided with an SiO_x barrier layer protected by a protective coating or layer wherever it is in contact or likely to be in contact with a fluid pharmaceutical composition contained in the syringe. An advantage of this construction is that the protective coating or layer, which is in contact with the fluid pharmaceutical composition when the syringe is stored prefilled, can be optimized for protection of the SiO_x barrier layer, while the lubricity layer, which is located where the plunger typically contacts the inner surface **264** at a fixed location during storage, can be optimized for lubricity. The lubricity coating or layer on the plunger is in the right position to prevent "sticktion" during storage and to continue to lower the friction between the plunger and barrel when the plunger is advanced, and if applied by CVD is contemplated to be less subject to displacement by the force exerted by the plunger on the barrel than traditional silicon oil coatings or layers and more uniformly applied as a uniform coating rather than as isolated droplets of liquid. As a further option, an adhesion

layer or coating of SiO_xC_y can be applied to the substrate and the barrier layer can be applied to the adhesion layer to improve adhesion of the SiO_x barrier layer or coating to the substrate.

A concern of converting from glass to plastic syringes centers around the potential for leachable materials from plastics. With plasma coating technology, the coatings or layers derived from non-metal gaseous precursors, for example HMDSO or OMCTS or other organosilicon compounds, will itself contain no trace metals and function as a barrier to inorganic, metals and organic solutes, preventing leaching of these species from the coated substrate into syringe fluids. In addition to leaching control of plastic syringes, the same plasma protective coating or layer technology offers potential to provide a solute barrier to the plunger tip, typically made of elastomeric plastic compositions containing even higher levels of leachable organic oligomers and catalysts.

Moreover, certain syringes prefilled with synthetic and biological pharmaceutical formulations are very oxygen and moisture sensitive. A critical factor in the conversion from glass to plastic syringe barrels will be the improvement of plastic oxygen and moisture barrier performance. The plasma protective coating or layer technology is suitable to maintain the SiO_x barrier coating or layer for protection against oxygen and moisture over an extended shelf life.

Even another embodiment is a plunger **258** for a syringe **252**, comprising a piston or tip, a protective coating or layer, and a push rod. The piston or tip has a front face, a generally cylindrical side face that slides within the barrel **250**, comprising a substrate, and a back portion. The side face is configured to movably seat within a syringe barrel. The protective coating or layer is on the substrate and is a lubricity and/or protective coating interfacing with the side face. The lubricity and/or protective coating is produced from a chemical vapor deposition (CVD) process employing the previously defined precursor feed or process gas. The push rod engages the back portion of the piston and is configured for advancing the piston in a syringe barrel.

Even another embodiment is a medical or diagnostic kit including a vessel having a coating or layer as defined in any embodiment herein on a substrate as defined in any embodiment above. Optionally, the kit additionally includes a medicament or diagnostic agent which is contained in the vessel with a protective coating in contact with the coating or layer; and/or a hypodermic needle, double-ended needle, or other delivery conduit; and/or an instruction sheet.

Other aspects of the invention include any one or more of the following:

Use of the protective coating or layer according to any embodiment described above for treating a surface and thereby preventing or reducing mechanical and/or chemical effects of the surface on a compound or composition in contact with the protective coating or layer;

Use of the coating or layer according to any described embodiment as a lubricity and/or protective coating;

Use of the coating or layer according to any described embodiment for protecting a compound or composition contacting the protective coating or layer against mechanical and/or chemical effects of the surface of the vessel material without a protective coating;

Use of the coating or layer according to any described embodiment for preventing or reducing precipitation and/or clotting or platelet activation of a compound or a component of the composition in contact with the coating or layer.

As one option, the compound or a component of the composition is insulin, and precipitation of the insulin is prevented or reduced. As another option, the compound or a component of the composition is blood or a blood fraction, and blood clotting or platelet activation is prevented or reduced. As still another option, the vessel with a protective coating is a blood collection tube. Optionally, the blood collection tube can contain an agent for preventing blood clotting or platelet activation, for example ethylenediaminetetraacetic acid (EDTA), a sodium salt thereof, or heparin.

Additional options for use of the invention include any one or more of the following:

Use of a coated substrate according to any described embodiment, for example a vessel such as a sample collection tube, for example a blood collection tube and/or a closed-ended sample collection tube; a vial; a conduit; a cuvette; or a vessel part, for example a stopper; or a syringe, or a syringe part, for example a barrel or piston for reception and/or storage and/or delivery of a compound or composition.

The use of a coated substrate according to any described embodiment is contemplated for storing insulin.

The use of a coated substrate according to any described embodiment is contemplated for storing blood. Optionally, the stored blood is viable for return to the vascular system of a patient.

Use of a coating or layer according to any described embodiment is contemplated as (i) a lubricity coating having a lower frictional resistance than the uncoated surface; and/or (ii) a protective coating preventing dissolution of the barrier coating in contact with a fluid, and/or (iii) a hydrophobic layer that is more hydrophobic than the uncoated surface.

Other aspects of the invention include any of the uses defined above in the summary section.

DETAILED DESCRIPTION

The following is a more detailed description of the invention. It starts with a general description of the present invention, then describes the equipment suitable to prepare the protective coating or layer of the present invention and subsequently describes the protective coating or layer embodiments, the coated pharmaceutical packages or other vessels, and the methods for their production.

Substrate

The substrate of the protective coating or layer in any embodiment is typically a vessel having a surface made of plastic (for example the inner or interior surface of a plastic syringe or vial). Typical plastic substrates are listed elsewhere in the present description and in referenced patents. Particularly suitable substrates in the context of the present invention are COC (cyclic olefin copolymer), COP (cyclic olefin polymer), PET (polyethylene terephthalate), and polypropylene, with COC being specifically suitable.

Barrier Layer

The barrier coating or layer for any embodiment defined in this specification (unless otherwise specified in a particular instance) is a coating or layer, optionally applied by PECVD as indicated in U.S. Pat. No. 7,985,188. The barrier layer optionally is characterized as an "SiO_x" coating, and contains silicon, oxygen, and optionally other elements, in which x, the ratio of oxygen to silicon atoms, is from about 1.5 to about 2.9, or 1.5 to about 2.6, or about 2. These alternative definitions of x apply to any use of the term SiO_x in this specification. The barrier coating or layer is applied, for example to the interior of a pharmaceutical package or other vessel, for example a sample collection tube, a syringe barrel, a vial, or another type of vessel.

Protective Layer

The protective layer is applied over at least a portion of the SiO_x layer to protect the SiO_x layer from contents stored in a vessel, where the contents otherwise would be in contact with the SiO_x layer.

Precursors for Protective Coating or Layer

The present lubricating or protective coating or layer is a saccharide coupled to the SiO_x barrier layer by a substituted silane coupling agent.

The silane coupling agent can be, for example, trimethoxysilylpropyl isocyanate. The silane functional group interacts with an SiO_x barrier layer. The isocyanate functional group reacts with a hydroxyl group of the saccharide to provide a urethane linkage. The coupling agent thus functions to anchor the saccharide, which provides a lubricated surface in an aqueous environment, in this case the contents of the container, to the barrier layer to prevent the saccharide from dispersing in the aqueous environment.

The silane coupling agent can instead be, for example, 3-Aminopropyltriethoxysilane (APTES). The silane functional group interacts with an SiO_x barrier layer. The amino functional group reacts with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) and N-hydroxysulfosuccinimide (NHS) in the presence of haluronic acid (HA). EDC/NHS can chemically graft HA onto APTES.

The coupling agent thus functions to anchor the saccharide, which provides a lubricated surface in an aqueous environment, in this case the contents of the container, to the barrier layer to prevent the saccharide from dispersing in the aqueous environment.

The saccharide precursor for use to provide a protective coating or layer is contemplated to be a water soluble or dispersible saccharide, dispersed or dissolved in water. The precursor may be present as from about 0.05% to about 15% by weight, or from about 0.2 to about 10% by weight, or from about 0.5% to about 6% by weight, or from about 1.5% to about 3% by weight, of the composition.

The saccharide can be selected from the group consisting of mono- and polysaccharides (or, more broadly, carbohydrates) and their derivatives. Saccharide (which for the present purpose includes disaccharide and higher saccharide) materials contemplated for use herein include any sugar, for example sorbitan, corn starch, other starches, and saccharide gums. Saccharide gums contemplated for use herein include agar, Arabic, xanthan (for example, KELZAN industrial grade xanthan gum, available from the Kelco Div. of Merck & Co, Inc. of Rahway, N.J.), pectin, alginate, tragacanath, dextran, and other gums. Derivative saccharides contemplated for use herein include cellulose acetates, cellulose nitrates, methylcellulose, and carboxymethylcellulose. Hemi-cellulose saccharides contemplated for use herein include d-gluco-d-mannans, d-galacto-d-gluco-d-mannans, and others. Haluronic acid is also specifically contemplated, as is sorbitan.

Also contemplated herein as saccharides are alkylcelluloses or carboxyalkylcelluloses, their low- and medium-viscosity alkali metal salts (e.g. sodium carboxymethylcellulose, or "CMC"), cellulose ethers, and nitrocellulose. Examples of such saccharides include KLUCEL hydroxypropylcellulose; AQUALON CMC 7L sodium carboxymethylcellulose, and NATROSOL hydroxyethylcellulose. These are all commercially available from Aqualon Company of Hopewell, Va. Saccharides contemplated herein further include ethylcellulose, available from Hercules of Wilmington, Del.; METHOCEL cellulose ethers, available from Dow Chemical Co., Midland, Mich.; and nitrocellulose, which is also available from Hercules.

Method of Applying a Lubricity Coating or Layer

A method of applying a lubricity coating or layer derived from an organosilicon precursor, and the resulting protective coating or layer and coated item are described for example in U.S. Pat. No. 7,985,188. A "lubricity coating" or any similar term is generally defined as a coating or layer that reduces the frictional resistance of the coated surface, relative to the uncoated surface, which can include a coating which is a saccharide or a coating as described in U.S. Pat. No. 7,985,188. If the coated object is a syringe (or syringe part, for example syringe barrel) or any other item generally containing a plunger or movable part in sliding contact with the coated surface, the frictional resistance has two main aspects—breakout force and plunger sliding force.

It should be understood that a coating optionally can be both a lubricity coating or layer and a protective coating or layer, respectively as explained in this description.

Barrier Coating or Layer

Any barrier coating or layer described in U.S. Patent No. 7,985,188 is contemplated for use in any embodiment of the present invention.

Measurement of Coating Thickness

The thickness of a coating or layer such as the protective coating or layer, the barrier coating or layer, the lubricity coating or layer, and/or a composite of any two or more of these layers can be measured, for example, by transmission electron microscopy (TEM). An exemplary TEM image for an SiO_2 barrier coating or layer is shown in FIG. **6**.

The TEM can be carried out, for example, as follows. Samples can be prepared for Focused Ion Beam (FIB) cross-sectioning in two ways. Either the samples can be first coated with a thin layer of carbon (50-100 nm thick) and then coated with a sputtered coating or layer of platinum (50-100 nm thick) using a K575X Emitech protective coating or layer system, or the samples can be coated directly with the protective sputtered Pt layer. The coated samples can be placed in an FEI FIB200 FIB system. An additional coating or layer of platinum can be FIB-deposited by injection of an organometallic gas while rastering the 30 kV gallium ion beam over the area of interest. The area of interest for each sample can be chosen to be a location half way down the length of the syringe barrel. Thin cross sections measuring approximately 15 μm ("micrometers") long, 2 μm wide and 15 μm deep can be extracted from the die surface using an in-situ FIB lift-out technique. The cross sections can be attached to a 200 mesh copper TEM grid using FIB-deposited platinum. One or two windows in each section, measuring about 8 μm wide, can be thinned to electron transparency using the gallium ion beam of the FEI FIB.

Cross-sectional image analysis of the prepared samples can be performed utilizing either a Transmission Electron Microscope (TEM), or a Scanning Transmission Electron Microscope (STEM), or both. All imaging data can be recorded digitally. For STEM imaging, the grid with the thinned foils can be transferred to a Hitachi HD2300 dedicated STEM. Scanning transmitted electron images can be acquired at appropriate magnifications in atomic number contrast mode (ZC) and transmitted electron mode (TE). The following instrument settings can be used.

Scanning Transmission Electron Microscope	
Instrument	
Manufacturer/Model	Hitachi HD2300

-continued

	Scanning Transmission Electron Microscope
Accelerating Voltage	200 kV
Objective Aperture	#2
Condenser Lens 1 Setting	1.672
Condenser Lens 2 Setting	1.747
Approximate Objective Lens Setting	5.86
ZC Mode Projector Lens	1.149
TE Mode Projector Lens	0.7
Image Acquisition	
Pixel Resolution	1280 × 960
Acquisition Time	20 sec.(×4

For TEM analysis the sample grids can be transferred to a Hitachi HF2000 transmission electron microscope. Transmitted electron images can be acquired at appropriate magnifications. The relevant instrument settings used during image acquisition can be those given below.

Instrument	Transmission Electron Microscope
Manufacturer/Model	Hitachi HF2000
Accelerating Voltage	200 kV
Condenser Lens 1	0.78
Condenser Lens 2	0
Objective Lens	6.34
Condenser Lens Aperture	#1
Objective Lens Aperture for imaging	#3
Selective Area Aperture for SAD	N/A

Liquid-applied Protective Coating or Layer

Another example of a suitable barrier or other type of protective coating or layer, usable in conjunction with the PECVD-applied protective coating or layer or other PECVD treatment as disclosed here, can be a liquid barrier, lubricant, surface energy tailoring, or protective coating or layer **90** applied to the inner or interior surface of a pharmaceutical package or other vessel, either directly or with one or more intervening PECVD-applied coatings or layers described in this specification, for example SiO_x, a lubricity coating or layer and/or a protective coating or layer, or both.

A suitable liquid barrier, lubricity, or protective coating or layer **90** also optionally can be applied, for example, by applying a liquid monomer or other polymerizable or curable material to the inner or interior surface of the vessel **80** and curing, polymerizing, or crosslinking the liquid monomer to form a solid polymer, or by applying a solvent-dispersed polymer to the surface **88** and removing the solvent.

Any of the above methods can include as a step forming a protective coating or layer **90** on the interior **88** of a vessel **80** via the vessel port **92** at a processing station or device **28**. One example is applying a liquid protective coating or layer, for example of a curable monomer, prepolymer, or polymer dispersion, to the inner or interior surface **88** of a vessel **80** and curing it to form a film that physically isolates the contents of the vessel **80** from its inner or interior surface **88**. The prior art describes polymer protective coating or layer technology as suitable for treating plastic blood collection tubes. For example, the acrylic and polyvinylidene chloride (PVdC) protective coating materials and methods described in U.S. Pat. No. 6,165,566, which is hereby incorporated by reference, optionally can be used.

Any of the above methods can also include as a step forming a coating or layer on the exterior outer wall of a vessel **80**. The exterior coating or layer optionally can be a barrier coating or layer, optionally an oxygen barrier coating or layer, or optionally a water barrier coating or layer. The exterior coating or layer can also be an armor layer that protects the outer wall of a vessel **80**. One example of a suitable exterior coating or layer is polyvinylidene chloride, which functions both as a water barrier and an oxygen barrier. Optionally, the exterior coating or layer can be applied as a water-based coating or layer. The exterior coating or layer optionally can be applied by dipping the vessel in it, spraying it on the pharmaceutical package or other vessel, or other expedients.

PECVD Treated Pharmaceutical Packages or Other Vessels Coated Pharmaceutical Packages or Other Vessels

Pharmaceutical packages or other vessels, such as a prefilled syringe (schematically shown in FIG. **7**) or a vial (schematically shown in FIGS. **8** and **9**) are contemplated having a barrier coating or layer such as **288** at least partially covered by a protective coating or layer such as **286**.

The pharmaceutical package **210** as shown in any embodiment, for example FIGS. **7** TO **9**, comprises a vessel or vessel part such as **250**; optionally a barrier coating or layer such as **288** on the vessel or vessel part; a protective coating or layer such as **286** on the vessel, vessel part, or barrier coating or layer; and a pharmaceutical composition or preparation such as **218** contained within the vessel.

The barrier coating or layer such as **288** can be an SiO_x barrier coating or layer applied as described in any embodiment of this specification or in U.S. Pat. No. 7,985,188. For example, the barrier coating or layer such as **288** of any embodiment can be applied at a thickness of at least 2 nm, or at least 4 nm, or at least 7 nm, or at least 10 nm, or at least 20 nm, or at least 30 nm, or at least 40 nm, or at least 50 nm, or at least 100 nm, or at least 150 nm, or at least 200 nm, or at least 300 nm, or at least 400 nm, or at least 500 nm, or at least 600 nm, or at least 700 nm, or at least 800 nm, or at least 900 nm. The barrier coating or layer can be up to 1000 nm, or at most 900 nm, or at most 800 nm, or at most 700 nm, or at most 600 nm, or at most 500 nm, or at most 400 nm, or at most 300 nm, or at most 200 nm, or at most 100 nm, or at most 90 nm, or at most 80 nm, or at most 70 nm, or at most 60 nm, or at most 50 nm, or at most 40 nm, or at most 30 nm, or at most 20 nm, or at most 10 nm, or at most 5 nm thick. Specific thickness ranges composed of any one of the minimum thicknesses expressed above, plus any equal or greater one of the maximum thicknesses expressed above, are expressly contemplated. The thickness of the SiO_x or other barrier coating or layer can be measured, for example, by transmission electron microscopy (TEM), and its composition can be measured by X-ray photoelectron spectroscopy (XPS). The protective coating or layer described herein can be applied to a variety of pharmaceutical packages or other vessels made from plastic or glass, for example to plastic tubes, vials, and syringes.

The protective coating or layer such as **286** can be a saccharide protective coating or layer applied as described in any embodiment of this specification.

Vessel Made of Glass

Another embodiment is a pharmaceutical package **210** as shown in any embodiment, for example FIGS. **7** TO **9**, comprising a vessel or vessel part such as **214** or **250** made of glass; optionally a barrier coating or layer such as **288** on the vessel or vessel part; a protective coating or layer such as **286** on the vessel, vessel part, or barrier coating or layer; and a pharmaceutical composition or preparation such as

218 contained within the vessel. In this embodiment the barrier coating or layer is optional because a glass vessel wall in itself is an extremely good barrier layer. It is contemplated to optionally provide a barrier layer primarily to provide isolation: in other words, to prevent contact and interchange of material of any kind, such as ions of the glass or constituents of the pharmaceutical composition or preparation between the vessel wall and the contents of the vessel. The protective layer as defined in this specification is contemplated to perform the isolation function independently, at least to a degree. This protection layer is contemplated to provide a useful function on glass in contact with the pharmaceutical composition or preparation, as the present working examples show that borosilicate glass, commonly used today for pharmaceutical packaging, is dissolved by a fluid composition having a pH exceeding 5. Particularly in applications where such dissolution is disadvantageous or perceived to be disadvantageous, the present protective coatings or layers will find utility.

The vessel can be made, for example of glass of any type used in medical or laboratory applications, such as soda-lime glass, borosilicate glass, or other glass formulations. One function of a protective coating or layer on a glass vessel can be to reduce the ingress of ions in the glass, either intentionally or as impurities, for example sodium, calcium, or others, from the glass to the contents of the pharmaceutical package or other vessel, such as a reagent or blood in an evacuated blood collection tube. Alternatively, a dual functional protective/lubricity coating or layer can be used on a glass vessel in whole or in part, such as selectively at surfaces contacted in sliding relation to other parts, to provide lubricity, for example to ease the insertion or removal of a stopper or passage of a sliding element such as a piston in a syringe, as well as to provide the isolation of a protective coating or layer. Still another reason to coat a glass vessel, for example with a dual functional hydrophobic and protective coating or layer, is to prevent a reagent or intended sample for the pharmaceutical package or other vessel, such as blood, from sticking to the wall of the vessel or an increase in the rate of coagulation of the blood in contact with the wall of the vessel, as well as to provide the isolation of a protective coating or layer.

A related embodiment is a vessel as described in the previous paragraphs, in which the barrier coating or layer is made of soda lime glass, borosilicate glass, or another type of glass coating or layer on a substrate.

Vessels Generally

A vessel with a protective coating as described herein and/or prepared according to a method described herein can be used for reception and/or storage and/or delivery of a compound or composition. The compound or composition can be sensitive, for example air-sensitive, oxygen-sensitive, sensitive to humidity and/or sensitive to mechanical influences. It can be a biologically active compound or composition, for example a pharmaceutical preparation or medicament like insulin or a composition comprising insulin. In another aspect, it can be a biological fluid, optionally a bodily fluid, for example blood or a blood fraction. In certain aspects of the present invention, the compound or composition can be a product to be administrated to a subject in need thereof, for example a product to be injected, like blood (as in transfusion of blood from a donor to a recipient or reintroduction of blood from a patient back to the patient) or insulin.

A vessel with a protective coating as described herein and/or prepared according to a method described herein can further be used for protecting a compound or composition contained in its interior space against mechanical and/or chemical effects of the surface of the vessel material. For example, it can be used for preventing or reducing precipitation and/or clotting or platelet activation of the compound or a component of the composition, for example insulin precipitation or blood clotting or platelet activation.

It can further be used for protecting a compound or composition contained in its interior against the environment outside of the pharmaceutical package or other vessel, for example by preventing or reducing the entry of one or more compounds from the environment surrounding the vessel into the interior space of the vessel. Such environmental compound can be a gas or liquid, for example an atmospheric gas or liquid containing oxygen, air, and/or water vapor.

A vessel with a protective coating as described herein can also be evacuated and stored in an evacuated state. For example, the protective coating or layer allows better maintenance of the vacuum in comparison to a corresponding vessel without a protective coating. In one aspect of this embodiment, the vessel with a protective coating is a blood collection tube. The tube can also contain an agent for preventing blood clotting or platelet activation, for example EDTA or heparin.

Any of the above-described embodiments can be made, for example, by providing as the vessel a length of tubing from about 1 cm to about 200 cm, optionally from about 1 cm to about 150 cm, optionally from about 1 cm to about 120 cm, optionally from about 1 cm to about 100 cm, optionally from about 1 cm to about 80 cm, optionally from about 1 cm to about 60 cm, optionally from about 1 cm to about 40 cm, optionally from about 1 cm to about 30 cm long, and processing it with a probe electrode as described below. Particularly for the longer lengths in the above ranges, it is contemplated that relative motion between the probe and the vessel can be useful during protective coating or layer formation. This can be done, for example, by moving the vessel with respect to the probe or moving the probe with respect to the vessel.

In these embodiments, it is contemplated that the barrier coating or layer can be thinner or less complete than would be preferred to provide the high gas barrier integrity needed in an evacuated blood collection tube. In these embodiments, it is contemplated that the protective coating or layer can be thinner or less complete than would be preferred to provide the long shelf life needed to store a liquid material in contact with the barrier layer for an extended period.

As an optional feature of any of the foregoing embodiments the vessel has a central axis.

As an optional feature of any of the foregoing embodiments the vessel wall is sufficiently flexible to be flexed at least once at 20° C., without breaking the wall, over a range from at least substantially straight to a bending radius at the central axis of not more than 100 times as great as the outer diameter of the vessel.

As an optional feature of any of the foregoing embodiments the bending radius at the central axis is not more than 90 times as great as, or not more than 80 times as great as, or not more than 70 times as great as, or not more than 60 times as great as, or not more than 50 times as great as, or not more than 40 times as great as, or not more than 30 times as great as, or not more than 20 times as great as, or not more than 10 times as great as, or not more than 9 times as great as, or not more than 8 times as great as, or not more than 7 times as great as, or not more than 6 times as great as, or not more than 5 times as great as, or not more than 4 times as

great as, or not more than 3 times as great as, or not more than 2 times as great as, or not more than, the outer diameter of the vessel.

As an optional feature of any of the foregoing embodiments the vessel wall can be a fluid-contacting surface made of flexible material.

As an optional feature of any of the foregoing embodiments the vessel lumen can be the fluid flow passage of a pump.

As an optional feature of any of the foregoing embodiments the vessel can be a blood bag adapted to maintain blood in good condition for medical use.

As an optional feature of any of the foregoing embodiments the polymeric material can be a silicone elastomer or a thermoplastic polyurethane, as two examples, or any material suitable for contact with blood, or with insulin.

In an optional embodiment, the vessel has an inner diameter of at least 2 mm, or at least 4 mm.

As an optional feature of any of the foregoing embodiments the vessel is a tube.

As an optional feature of any of the foregoing embodiments the lumen has at least two open ends.

Vessel Containing Viable Blood, Having a Protective Coating or Layer Deposited from an Organosilicon Precursor

Even another embodiment is a blood containing vessel. Several non-limiting examples of such a vessel are a blood transfusion bag, a blood sample collection vessel in which a sample has been collected, the tubing of a heart-lung machine, a flexible-walled blood collection bag, or tubing used to collect a patient's blood during surgery and reintroduce the blood into the patient's vasculature. If the vessel includes a pump for pumping blood, a particularly suitable pump is a centrifugal pump or a peristaltic pump. The vessel has a wall; the wall has an inner or interior surface defining a lumen. The inner or interior surface of the wall has an at least partial protective coating or layer of a protective layer, which optionally also presents a hydrophobic surface. The protective coating or layer can be as thin as monomolecular thickness or as thick as about 1000 nm. The vessel contains blood viable for return to the vascular system of a patient disposed within the lumen in contact with the hydrophobic layer.

An embodiment is a blood containing vessel including a wall and having an inner or interior surface defining a lumen. The inner or interior surface has an at least partial protective coating or layer that optionally also presents a hydrophobic surface. The protective coating or layer can also comprise or consist essentially of SiO_xC_y, where x and y are as defined in this specification. The thickness of the hydrophobic coating or layer is within the range from monomolecular thickness to about 1000 nm thick on the inner or interior surface. The vessel contains blood viable for return to the vascular system of a patient disposed within the lumen in contact with the hydrophobic coating or layer.

Common Conditions for All Embodiments

In any embodiment contemplated here, many common conditions can be used, for example any of the following, in any combination. Alternatively, any different conditions described elsewhere in this specification or claims can be employed.

I. Coating Receiver of any Embodiment

Vessel of Any Embodiment

The vessel can be a sample collection tube, for example a blood collection tube, or a syringe, or a syringe part, for example a barrel or piston or plunger; a vial; a conduit; or a cuvette. The substrate can be a closed-ended tube, for example a medical sample collection tube. The substrate can be the inside wall of a vessel having a lumen, the lumen having a void volume of from 0.5 to 50 mL, optionally from 1 to 10 mL, optionally from 0.5 to 5 mL, optionally from 1 to 3 mL. The substrate surface can be part or all of the inner or interior surface of a vessel having at least one opening and an inner or interior surface, and wherein the gaseous reactant, also known in any embodiment as a precursor feed, fills the interior lumen of the vessel and the plasma can be generated in part or all of the interior lumen of the vessel.

Syringe and Parts

The substrate can be a syringe barrel. The syringe barrel can have a plunger sliding surface and the protective coating or layer can be disposed on at least a portion of the plunger sliding surface. The protective coating or layer can be a lubricity and/or protective coating. The lubricity and/or protective coating or layer can be on the barrel inner or interior surface. The lubricity and/or protective coating or layer can be on the plunger. In a particular aspect, the substrate is a staked needle syringe or part of a staked needle syringe.

Vessel to Receive Stopper

The substrate can be a stopper receiving surface in the mouth of a vessel. The substrate can be a generally conical or cylindrical inner or interior surface of an opening of a vessel adapted to receive a stopper.

Stopper

The substrate can be a sliding surface of a stopper. The substrates can be coated by providing a multiplicity of the stoppers located in a single substantially evacuated vessel. The chemical vapor deposition can be plasma-enhanced chemical vapor deposition and the stopper can be contacted with the plasma. The chemical vapor deposition can be plasma-enhanced chemical vapor deposition. The plasma can be formed upstream of the stopper, producing plasma product, and the plasma product can be contacted with the stopper.

A closure can define a substrate coated with a protective coating or layer, optionally a stopper coated with a lubricity and/or protective coating. The substrate can be a closure seated in a vessel defining a lumen and a surface of the closure facing the lumen can be coated with the protective coating or layer.

The protective coating or layer can be effective to reduce the transmission of a metal ion constituent of the stopper into the lumen of the vessel.

Substrate of Any Embodiment

The substrate can be a vessel wall. A portion of the vessel wall in contact with a wall-contacting surface of a closure can be coated with the protective coating or layer. The protective coating or layer can be a composite of material having first and second layers. The first coating or layer can interface with the elastomeric stopper. The first layer of the protective coating or layer can be effective to reduce the transmission of one or more constituents of the stopper into the vessel lumen. The second protective coating or layer can interface with the inner wall of the vessel. The second layer can be effective to reduce friction between the stopper and the inner wall of the vessel when the stopper is seated on the vessel.

Alternatively, the first and second layers of any embodiment can be defined by a protective coating or layer of graduated properties containing carbon and hydrogen, in which the proportions of carbon and hydrogen are less in the first coating or layer (applied to the substrate) than in the second coating or layer (exposed to the contents of the vessel).

The protective coating or layer of any embodiment can be applied by plasma enhanced chemical vapor deposition.

The substrate of any embodiment can comprise glass, alternatively a polymer, alternatively a polycarbonate polymer, alternatively an olefin polymer, alternatively a cyclic olefin copolymer, alternatively a polypropylene polymer, alternatively a polyester polymer, alternatively a polyethylene terephthalate polymer, alternatively a polyethylene naphthalate polymer, alternatively a combination, composite or blend of any two or more of the above materials.

EXAMPLE

Polysaccharide-Grafted SiO_x-Coated Plastic Syringe Barrel

3-Aminopropyltriethoxysilane (APTES) grafting. (Method 1-Step 1)

To a freshly SiO_x-plasma coated COP syringe 1 mL staked needle syringe barrel, under vacuum, APTES (Sigma-Aldrich) vapor is pumped through the syringe barrel and allowed to react with and be deposited on the SiO_x surface for 2 h, ideally resulting in a monolayer. During the reaction, a low pressure is maintained to minimize the condensation of microscopic droplets of APTES on the surfaces. Following the deposition, covalent APTES grafting was done by annealing the surface in a vacuum oven for 30 min at 80° C.

Haluronic Acid (HA) Grafting (Method 1-Step 2)

A 3 mg/mL HA (average MW=1.6 MDa, Sigma-Aldrich) solution is put into the APTES-grafted SiO_x surface barrel interior for 3 h. The right amounts of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) and N-hydroxysulfosuccinimide (NHS) (Sigma-Aldrich) were added into the HA solution to bring the EDC and NHS concentrations to 1 M for each component (50/50 EDC/NHS mixture). EDC/NHS can chemically graft HA onto APTES as well as cross-link the grafted HA layer, forming a gel-like HA layer. The interior syringe barrel surface is then rinsed thoroughly using phosphate buffered saline (PBS) buffer and capped to prevent dessication of bound water to the grafted polysaccharide.

Adapted from Jing Yu, Xavier Banquy, George W. Greene, Daniel D. Lowrey, and Jacob N. Israelachvili, *The Boundary Lubrication of Chemically Grafted and Cross-Linked Hyaluronic Acid in Phosphate Buffered Saline and Lipid Solutions Measured by the Surface Forces Apparatus*, Langmuir 2012, 28, 2244-2250, Department of Chemical Engineering and Materials Department, University of California, Santa Barbara, Calif. 93106.

While the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive; the invention is not limited to the disclosed embodiments. Other variations to the disclosed embodiments can be understood and effected by those skilled in the art and practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims. In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

The invention claimed is:

1. A filled package comprising: a vessel having a lumen defined at least in part by a wall, the wall having an interior surface facing the lumen and an outer surface; a barrier coating of SiO_x, wherein x is from 1.5 to 2.9, from 2 to 1000 nm thick, the barrier coating of SiO_x having an interior surface facing the lumen and an outer surface facing the wall interior surface, the barrier coating being effective to reduce the ingress of atmospheric gas into the lumen compared to an vessel without a barrier coating; a protective coating of a saccharide, the protective coating of a saccharide having an interior surface facing the lumen and an outer surface facing the interior surface of the barrier coating, the protective coating of a saccharide being effective to increase the calculated shelf life of the package (total Si/Si dissolution rate); and a fluid composition contained in the lumen and having a pH between 5 and 9; wherein the calculated shelf life of the package is more than six months at a storage temperature of 4° C.

2. The filled package of claim **1**, in which at least a portion of the wall of the vessel comprises: a polyolefin, a polyester or a combination of a polyolefin and a polyester.

3. The filled package of claim **1**, in which at least a portion of the wall of the vessel comprises or consists essentially of a member selected from the group consisting of: a cyclic olefin polymer, a cyclic olefin copolymer, polypropylene, a polyester and polyethylene terephthalate.

4. The filled package of claim **1**, in which the vessel comprises a syringe barrel or a vial.

5. The filled package of claim **1** in which the protective coating of a saccharide further comprises a coupling agent linking the protective coating of a saccharide to the SiO_x barrier coating.

6. The filled package of claim **5**, in which the protective coating of a saccharide is a sugar that is a sorbitan or comprises hyaluronic acid.

7. The filled package of claim **5**, in which the coupling agent has a functionality reactive with a saccharide hydroxyl functional group.

8. The filled package of claim **5**, in which the coupling agent comprises a member selected from the group consisting of: a silane functional group that interacts with an SiO_x barrier layer, trimethoxysilylpropyl isocyanate, and 3-Aminopropyltriethoxysilane (APTES).

9. The filled package of claim **1**, in which the protective coating of a saccharide contacting the fluid composition is between 10 and 1000 nm thick two years after the filled package is assembled.

10. The filled package of claim **1**, in which the rate of erosion of the protective coating of a saccharide, if directly contacted by a fluid composition having a pH of 8, is less than 20% of the rate of erosion of the barrier coating, if directly contacted by the same fluid composition under the same conditions.

11. The filled package of claim **1**, in which the rate of erosion of the protective coating of a saccharide, if directly contacted by a fluid composition having a pH of 8, is from 5% to 20% of the rate of erosion of the barrier coating, if directly contacted by the same fluid composition under the same conditions.

12. The filled package of claim **1**, in which the protective coating of a saccharide is at least coextensive with the barrier coating.

13. The filled package of claim **1**, having a shelf life, after the filled package is assembled, of at least two years, in which the shelf life is determined at 4° C.

14. The filled package of claim **1**, having a shelf life, after the filled package is assembled, of at least two years, in which the shelf life is determined at 20° C.

15. The filled package of claim **1**, in which the fluid composition removes the protective coating of a saccharide at a rate of 1 nm or less of thickness per 44 hours of contact with the fluid composition.

16. The filled package of claim **1**, in which the protective coating of a saccharide is effective to provide a lower frictional resistance than the uncoated interior surface, wherein the frictional resistance is reduced by at least 25% in comparison to the uncoated interior surface.

17. The filled package of claim **16** which is a syringe comprising a syringe barrel and a plunger and the wall defines at least a portion of the syringe barrel, in which the protective coating of a saccharide is effective to reduce the frictional resistance between the wall and the plunger at least two years after the filled package is assembled.

18. The filled package of claim **1**, in which the silicon dissolution rate by a 50 mM potassium phosphate buffer diluted in water for injection, adjusted to pH 8 with concentrated nitric acid, and containing 0.2 wt. % polysorbate-80surfactant from the vessel is less than 170 ppb/day.

19. The filled package of claim **1**, in which the total silicon content of the protective coating of a saccharide and barrier coating, upon dissolution into 0.1 N potassium hydroxide aqueous solution at 40° C. from the vessel, is less than 66 ppm.

20. The filled package of claim **1**, in which the calculated shelf life (total Si/Si dissolution rate) is more than 2 years.

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